The Journal of NSF-DBA Issue 23 EU Winter 2012/13

NSF DBA℠

Supply Chain

www.nsf-dba.com

welcome

Bob Pietrowski
Managing Partner
NSF-DBA

Welcome to the latest edition of the NSF-DBA Journal. You will see that this Journal has a strong focus on one of the most important issues facing the health science industry today – ensuring the integrity of the supply chain.

The health and wellbeing of patients worldwide is currently being threatened by two serious (potentially deadly) criminal activities: the deliberate adulteration of active ingredients and starting materials and the illegal manufacture and supply of counterfeit healthcare products, both for financial gain and with absolutely no regard for human safety. The fight against these illegal activities requires the active participation of organisations at many different levels and in many different countries. Foremost in this struggle will be the regulatory agencies and, of course, the reputable manufacturers.

In this issue, Pete Gough describes how regulators in the European Union have responded to the threat of adulterated starting materials and the huge challenges that recent and impending regulations pose for manufacturers of healthcare products, while Mike Halliday describes how our services can assist you in assuring the integrity of your supply chain.

Elsewhere in this issue we welcome the latest version of Annex 2, but question why it took so long to produce, and we include all the usual features: the latest Industry News, our training courses for the first 3 months of 2013, QP Update and the latest additions to our ever-expanding team of consultants in mainland Europe.

We hope you enjoy this latest edition of the Journal.

Bob Pietrowski
Managing Partner

NSF DBA The Health Sciences, Training, Consultancy and Auditing Experts SM

Tech Talk

Supply Chain Assurance

As the European Union tries to get a grip with counterfeit medicinal products through legislation, Pete Gough discusses the headache globalisation of pharmaceutical API manufacture is causing to the industry

The discovery of contaminated Heparin in 2008 focused global attention on the need for greater security of pharmaceutical supply chains. Preceding this there had been a worrying increase in the number of counterfeit medicinal products reaching legitimate supply chains but it was the Heparin incident that really brought the issues into sharp focus. Since 2008 various events have only confirmed that there are real risks to patients from deliberate adulteration and counterfeiting of medicines or their ingredients; e.g. melamine in milk, chromium in gelatine, plasticisers in antibiotics, fake Avastin, to name but a few. It has been estimated that globally around 10% of medicinal products are counterfeit, however, the proportions are still much lower in the developed world but can be as high as 80% in parts of the third world.

In July 2011 the EU published Directive 2011/62/EU, the Falsified Medicines Directive (FMD) and in June 2012 the US Congress passed the FDA Safety and Innovation Act (FDASIA). Both of these far reaching pieces of legislation seek to impose much stronger controls on pharmaceutical supply chains and the implications for the manufacturers of medicinal products and their suppliers are very significant.

Looking at the FMD first, many of its provisions are sensible, proportionate and should provide increased safety for patients:

- Active Pharmaceutical Ingredient (API) supply to comply with Good Distribution Practice (GDP) as well as being made to GMP
- Excipients to be made to an appropriate level of GMP determined by a formal risk assessment
- The legal obligation for the users of APIs and excipients to map and audit their supply chains for GMP and GDP compliance
- The need for "importers, manufacturers and distributors of active substances" in the EU to register with the Competent Authority of the Member State where they operate and be required to submit at least annual reports of changes to the Authority
- The addition of "Safety Features" to packs of medicinal products

Unfortunately, the FMD also contains a requirement that has the potential to seriously reduce the availability of medicinal products in Europe and to drive even more medicinal product manufacturing out of the EU/EEA. This is the poorly thought through requirement that, from 2 July 2013, APIs shall only be imported if the active substances are accompanied by a written confirmation from the Competent Authority of the exporting third country, and the plant manufacturing the exported active substance confirms that the standards of GMP and control of the plant are equivalent to those in the EU.

By early November 2012 just five countries had applied to the Commission to be added to the list of countries exempt from the need for this certification; Switzerland, Israel, Australia, Singapore and Brazil. None of these had been approved at that time. Many countries have responded negatively to the

Tech talk

requirements from Europe seeking to impose this extra-territorial obligation on them. Even the EU's ICH partners, the USA and Japan, have yet to decide if they will be prepared to issue the required API certificates.

India and China are, reportedly, considering jointly referring this to the World Trade Organisation (WTO) as it constitutes a technical barrier to trade. S Eshwar Reddy, India's Deputy Drug Controller, was recently reported in the online newsletter in-Pharma Technologist.com as having stated that "If the importing country has specific GMP requirements, that is their responsibility to audit the facilities. It is the responsibility of the importing country, not the exporting country."

India is a major supplier of APIs to the EU and whilst it has indicated that it will set up an Authority to issue the required certificates it will do so on the basis of just a half-day visit to each API site, which while complying with the letter of the new requirement offers no real additional supply chain assurance.

This potentially means that after 2 July 2013 if a medicinal product manufacturer is unable to obtain the required certification for the API imported into the EU they will have to cease production of their product. This will potentially lead to the shortage of some medicines across the EU, which perversely may encourage counterfeiting to fill the gaps. It is possible that in their naivety the European Commission introduced this requirement in an attempt to drive more API manufacture within the EU. However, it is far too late for this as over the past 15 or so years much of the EU's infrastructure to manufacture APIs has closed and there is little prospect of significant re-investment in this area in the currently depressed economic climate. The more likely consequence is that companies will choose to also move their secondary manufacturing outside of the EU as the importation of fully finished medicinal products avoids the need for the certification of the API. This requirement can only do further damage to the pharmaceutical industry in Europe, which was once such a powerhouse of the European economy, but is now shrinking rapidly under an ever increasing burden of poorly thought through legislation coming from Brussels.

Most of the provisions of the FMD are sensible precautions to protect EU citizens from counterfeit products. It is a shame that the European Commission chose to try to impose their certification scheme for APIs on the rest of the world; it would have been far better to foster co-operation with foreign governments to try to defeat this immoral trade. The current certification requirement will almost certainly be ineffective and counterproductive, antagonising and annoying the rest of the world and driving even more medicinal product manufacturing overseas while providing little or no extra supply chain assurance.

The US FDASIA appears to be a better thought through piece of legislation, although there is still a lot of detail to be clarified in new rules and guidance from FDA. For a review of the FDASIA see the 'News' section on page 8 of this issue of the Journal.

One feature of both the European FMD and the US FDASIA is the introduction of a system to verify the authenticity of a medicinal product at the point of dispensing, what the EU has called "Safety Features" and the Americans call "Track and Trace". Both regions are working on this and it would certainly be helpful to the manufacturers of finished product if the requirements were, if not identical, at least similar. The implementation costs of these systems are going to have to be largely borne by the pharmaceutical industry. The industry literally could not afford to equip its packaging facilities to accommodate totally different systems in the EU and US. There have been good links forged between the EMA and the FDA over the past 10 years or so, hopefully, they will not develop totally different systems. Most people in the EU are expecting the system for adding the serialisation number to packs to be based on a 2D bar code as the most practical and economic option.

Concerns over pharmaceutical supply chains and the implementation of the new legislation requirements are set to dominate the industry for at least the next 5 years or more. This will add to the ever increasing burden on companies' audit systems and on the Qualified Persons who certify medicinal products for release.

NOTE: This Tech Talk on Supply Chain Assurance focuses on the start of the supply chain, ie purchasing of starting materials. Future Tech Talks will cover other aspects, eg Good Distribution Practice (GDP) and, when the Commission has decided how they will work, safety features.

NSF-DBA's four-day course on Active Pharmaceutical Ingredients will take place 17 to 20 June 2013

Your Partner in Supply Chain Assurance

Mike Halliday explains how our Unique Skills in Auditor Training and Third Party Auditing can help you Manage your Supply Chain

The current focus on supply chain integrity by international regulatory agencies and pharmaceutical manufacturers alike has placed huge emphasis on the importance of auditing as a key component of any supply chain assurance system.

We recently received our 200th booking for auditor training

Auditing vendors, suppliers, distribution networks, etc is both expensive and time-consuming, so companies want to 'do it once and do it right' (acknowledging that regular re-audits are a fact of life). Industry sector co-operative audit schemes such as Rx360 and EXCiPACT™ seemed, at one stage, to offer a convenient way of reducing the cost and burden of auditing by the sharing of audit reports prepared by independent bodies. However, such schemes have been slow to gather momentum as companies realise that, if they are to carry the liability for the starting materials and services they use, then they should carry out their own audits, using their own staff or independent auditors hired by them. This way, companies can dictate the scope, focus, standards, timing and duration of the audits and receive audit reports which enable them to take effective decisions regarding the quality of those products and services, rather than rely on a generic, 'off the shelf' audit report which may not focus on the products and processes important to them.

Last year we conducted over 100 audits worldwide

This is where NSF-DBA can help... by providing two essential services:

- **Training of auditors**
- **Independent, third party audits**

Auditor Training

When it comes to auditing, we should all remember the wise words of the never-to-be-forgotten 1980s pop group Bananarama… "it's not what you do, it's the way that you do it. That's what gets results." The way you plan your audit, the way you build rapport with the auditee, the way you ask questions, the way you listen to the answers, the way you assess risk and the way you make recommendations all have a profound effect on the value of the audit. It's not just about knowing the standards, although that is obviously important.

Our flagship training course, 'Effective Pharmaceutical Audits and Self-Inspections', is the first truly independently certified pharmaceutical GMP auditor training course. It is certified by IRCA, the world's largest international certification body for auditors of quality management systems. We introduced this course for the first time in 2012 and it has been an immediate success with the pharmaceutical industry. We have provided training through open courses in Europe, North America and South Africa and we recently received our 200th booking for the course – a great milestone considering the course has been available for less than a year and that numbers are restricted to 20! What is more, feedback from delegates attending the course has been fantastic – obviously we are doing something right and fulfilling a real need.

We Train Government Inspectors!

Further recognition of the excellence of the course came recently when a PIC/S member asked us to train all their GMP inspectors. This is an honour for us and we hope that our training will assist this national regulatory agency to harmonise its inspectional approach and to use risk assessment judiciously when inspecting manufacturers at home and abroad.

A PIC/S member country has asked us to train all their GMP inspectors

Two multinationals have contracted us to be their supplier audit team

Third Party Audits

Our carefully selected team of consultants have the experience and skills to perform effective audits of suppliers, distributors and all aspects of the modern pharmaceutical supply chain. What is more, we can perform high quality audits of products and processes that are specifically relevant to you, using standards that meet your needs. Perhaps that is why our clients contracted us to perform over a hundred audits on their behalf last year.

Two leading multinational pharmaceutical companies (one US-based and the other Japanese), realising that they did not have sufficient resource in-house to cover their auditing needs, hired us to become, in effect, their corporate supplier audit function. We performed audits of large and small suppliers and contractors all over the world and the two companies have been delighted with the service they received.

What we did for them, we can do for you too!

Delegates and tutors from our recent Manchester course.

Our auditor training course, 'Effective Pharmaceutical Audits and Self-Inspections', will next be held in Manchester on 20 to 24 May 2013.

We also hold regular short 'How To Audit…' courses which teach you how to audit specific activities such as API manufacture, computerised systems, etc. Visit www.nsf-dba.com for details.

If you would like to learn more about in-house auditor training or how we can assist you by performing supplier audits for you around the world, please contact our audit specialist Mike Halliday or Gill Gibbeson at the UK office.

Industry News

EU Pharma News

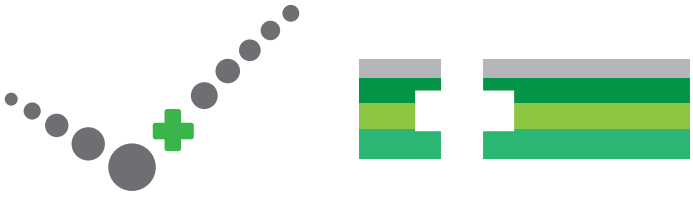
Falsified Medicines Directive – API Importation

Concerns over the implementation of the requirement that APIs imported from outside of the EU be accompanied by a certificate confirming compliance with EU GMP from the exporting country's Competent Authority continue to grow. Even the EU's ICH partners America and Japan appear to be reluctant to issue these certificates. We wonder whether European regulators truly understand that, unless they soften their demands regarding GMP certification of active ingredients, in 6 months' time many EU pharmaceutical companies will be out of business and the EU will be facing a catastrophic shortage of essential medicines.

Falsified Medicines Directive – Sales at a Distance (Internet Sales)

There is a whole range of new legal requirements governing what is called 'sales at a distance to the public', primarily aimed at controlling internet sales of medicinal products. One measure being introduced is a logo for approved internet sites.

On 17 October 2012 the Commission published a Concept Paper on the proposed internet controls. This provided two options for the proposed logo:



Good Pharmacovigilance Practice (GVP) Guidance

The EMA published the first batch of seven modules of GVP in June 2012, after a public consultation period from February to April 2012. It released modules III and X for consultation in June 2012 and modules IV and XV in July 2012. The full set of 16 final modules is scheduled to be available by early 2013.

The remaining five draft modules of the GVP package are under development and are scheduled for release for an eight-week public consultation during the fourth quarter of 2012.

EU GMP Guide Part 1

Revision of Chapter 1

The EU published the final version of the revision of Chapter 1 of Part I of the EU GMP Guide in September 2012 and is effective from 31 January 2013.

The title of Chapter 1 has been changed to 'Pharmaceutical Quality Systems' in order to integrate with the principles described in ICH Q10, which is published in Part III of the EU GMP Guide.

The draft changes issued in 2009 included numerous direct quotes from ICH Q10, but these are not included in the final version. However, it should be noted that by adding new requirements to Chapter 1 it will make them apply to veterinary medicinal products, as well as human products, in the EU, even though ICH Q10 has not been adopted by VICH.

The main changes in the revised Chapter 1 are in the areas of:

- The Pharmaceutical Quality System
- Continuous improvement and change management
- Supply chain management
- Senior management responsibilities
- Deviations and CAPA

The revised Chapter contains an extensive list of items that the Pharmaceutical Quality System (PQS) should ensure. Some of these items were listed in the previous version under the Quality Assurance section, but there are several new items that the PQS should ensure.

The new Chapter 1 states that *"Senior management has the ultimate responsibility to ensure an effective PQS is in place … senior management's leadership and active participation in the PQS is essential"*.

The need for periodic management review, with the involvement of senior management, is specified.

NSF-DBA will cover all these issues at the Quality Management Systems course, 8 to 12 April 2013.

Industry News

The final PQS expectation is that *"The Pharmaceutical Quality Systems should be defined and documented. A Quality Manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities"*.

The list of basic GMP requirements also has some additions:

- Significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented
- The distribution of products should take account of Good Distribution Practices

Together these changes are significant, but if a company has already made changes to their quality management systems to meet ICH Q10 then they should already comply with most of the new Chapter 1.

Revised Chapter 7 (Outsourced Activities)

In September 2012 the European Commission published the final version of the revision to this Chapter. The title of this Chapter has been changed from 'Contract Manufacture and Analysis' to 'Outsourced Activities', broadening it to cover any outsourced activity that, if performed in-house, is covered by the GMP Guide. The revised version became effective on 31 January 2012.

The principles of ICH Q10, Pharmaceutical Quality Systems, have been incorporated in this Chapter, consistent with the incorporation of these principles in other revised Chapters and Annexes of the EU GMP Guide.

The new section 7.8 states *"The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He should also ensure, either by himself, or based on the confirmation of the Contract Acceptor's Qualified Person, that all products and materials delivered to him by the Contract Acceptor have been processed in accordance with GMP and the marketing authorisation"*.

Annex 2: Biological Products

After issuing two draft versions since 2007 the final version was eventually published on 6 September 2012. This revised version is effective from 31 January 2013.

For a detailed review of the new Annex, see Bob Pietrowski's article in this Journal.

EU-Israel ACAA

On 23 October 2012 the European Parliament voted 379-230 with 41 abstaining in support of the Agreement on Conformity Assessment and Acceptance of Industrial Products (ACAA) between the EU and Israel. Medicinal products certified in the EU will be considered certified in Israel and vice versa under this, which is a protocol to the 1995 EU-Israel Association Agreement. It will apply to all pharmaceuticals except for advanced therapy products, special medicinal products based on tissues and cells of human origin, and medicinal products that include blood products.

An ACAA is a 'super' MRA, so may mean that imports from Israel will be able to be exempt from the need for re-testing on importation. The implementation date for this ACAA is not yet known.

ICH News

A Concept Paper is being prepared to justify the need to revise ICH Q7, the GMP Guide for active pharmaceutical ingredients, APIs.

PIC/S News

Japan and Korea have applied to join PIC/S.

At the PIC/S committee meeting in May 2012 Indonesia became the 41st member of PIC/S.

At this meeting several key decisions were made. One was to introduce a new sub-committee structure, which will be implemented by 1 January 2014. The second important decision was to establish new Working Groups in order to explore how to develop some new projects with the following objectives:

- Extending PIC/S' mandate to new activities such as Good Clinical Practices (GCP) and Good Pharmacovigilance Practices (GPP)
- Creating a PIC/S Inspectorate Academy to provide cost-efficient, primarily web-based, high quality harmonised training for Inspectorates

UK News

The legal framework for medicines legislation in the UK has undergone a major revision, with most of the 1968 Medicines Act disappearing. SI: 2012 No. 1916 'The Human Medicines Regulation 2012' (issued under the European Communities Act 1972) has been published and became effective on 14 August 2012.

On 18 October 2012 the MHRA published a consultation paper, MLX 379, on the transposition of Directive 2011/62/EU ('the Falsified Medicines Directive') into UK legislation. This document poses some 69 questions with responses sent to the MHRA by 19 November 2012. The consultation paper was accompanied by an 'Impact Assessment'.

USA News

FDA Organisation

In September 2012 the FDA announced that it is planning to reorganise its Office of Regulatory Affairs (ORA), including creating new offices and reorganising others, as it takes steps to remove cumbersome domestic and international distinctions and to keep up with increasingly global operations. The restructuring will also better position the ORA to address new legislative authorities included in the FDA Safety and Innovation Act (FDASIA).

In addition, CDER is looking to elevate the Office of Generic Drugs (OGD) into a 'super' office, a move necessitated by the recent passage of the Generic Drug User Fee Amendments (GDUFA) and a heightened US public focus on generic medicines.

The Food and Drug Administration Safety and Innovation Act (FDASIA)

The FDASIA was passed out of the US Congress on 26 June 2012. This new Act includes several major changes that will impact the pharmaceutical industry.

The FDASIA gives FDA the authority to collect user fees from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biologics. It also reauthorises two programmes that encourage paediatric drug development. This Act reauthorises the Prescription Drug User Fee Act (PDUFA), first enacted in 1992, and extends the scope of user fees to include generic drugs and biosimilar biologics for the first time.

There are two notable absences from the new FDASIA: one is that FDA was not given the authority that they sought from Congress to be able to order recalls, and the second is that there is no reference to 'track and trace'. However, on 25 October this year the US Senate's Health Education Labor and Pensions (HELP) Committee released a track and trace draft proposal. The proposal, if enacted, would give FDA the authority to work with industry to develop a national track and trace system.

As far as pharmaceutical manufacturers are concerned the section of the FDASIA that will have the greatest impact is Title VII, which is devoted to supply chain management. The main provisions of this title are:

- Removal of the requirement for biennial inspection of drug manufacturing sites and transition to a risk-based inspection frequency
- GMP now requires *"…managing the risk of and establishing the safety of raw materials used in the manufacturing of drugs, and finished drug products"*. Thus, failure to adequately control the supply chain of raw materials that are used in drug manufacture could result in the product being deemed adulterated
- FDA must establish good importer practices *"that specify the measures an importer shall take to ensure imported drugs are in compliance with the requirements of this Act and the Public Health Service Act"*
- Import of drugs will be barred if the manufacturer delays, denies, or limits an inspection, or refuses to permit entry or inspection
- Allows FDA to detain, for a certain period of time, any drugs found during an inspection that were thought to be adulterated or misbranded
- Allows FDA to take into account the inspections of a trusted foreign government when considering the risk of an establishment
- Requires commercial drug importers to register with FDA and submit a unique identifier for the principal place of business at the time of registration
- Greater penalties for counterfeiting drugs
  - 20 years' imprisonment or fine up to $1,000,000, or both
- Extraterritorial jurisdiction over any violation of the Federal Food, Drug and Cosmetic Act related to any article regulated under this Act if the article was intended to be imported into the US or if any act in furtherance of the violation was committed in the US

Some of the other changes introduced by Title VII FDASIA are:

- Company's drug listing to contain the name and place of business of each excipient manufacturer, including all establishments used in the production of the excipient, the unique facility identifier of each excipient establishment, and a point of contact mail address for each such excipient manufacturer
- For two years after the Secretary specifies a unique facility identifier system, the Secretary must maintain an electronic database. The database must allow FDA personnel the ability to search by any field of information or combination of fields submitted in a registration. The database must link to other relevant FDA databases
- Notification to FDA is required by a regulated person if the regulated person knows:
  - that use of a drug may result in serious injury or death
  - that there is a significant loss or known theft of such drug intended for use in the US
  - that the drug has been/is being counterfeited and the counterfeit product is in commerce in the US or could reasonably be expected to be introduced into commerce in the US, or the drug has been or is being imported into the US or may reasonably be expected to be offered for import into the US

In order to implement the FDASIA a number of FDA Rules and Guidances will need to be issued over the next few years, some of which have specified due dates, as listed below:

- Five Rules
  - Excipient information – no timeframe specified
  - Administrative destruction – final rule by 9 July 2014
  - Administrative detention – final rule by 9 July 2014
  - Standards of admission for imported drugs – final rule by 9 January 2014
  - Registration of commercial importers/GIPs – final rule by 9 July 2015
- Three Guidances
  - Specifying the Unique Facility Identifier (UFI) – no timeframe
  - Notification – no timeframe
  - Meaning of delay, limit, deny, refuse – guidance by 9 July 2013

James Pink, our Medical Device expert, explains the 2013 Training Programme

Course Series

The Medical Device team has opted to create a series of courses, delivered during a week to enable you to 'plug and play' your learning. Our series are broken down into Introductory, Practitioner and Advanced course formats. This means that you can choose to study some or all of the five days, thus furnishing you with an in-depth understanding of a particular QARA or technical subject.

Study Days

Our study days enable you to witness the very best in the industry coming together and working with you to resolve the most current concerns relating to specific topics in the field of medical device quality assurance and regulatory affairs. For example, our regulatory study days feature industry experts with at least 20 years' practical experience, coupled with the necessary authority to present their considered opinions, but this is countered by similar experienced regulatory professionals. We effectively get the 'truth' from all sides.

Workshops

Our Medical Device workshops are a unique opportunity for you to apply the theories and concepts often explained during training courses and for you to put them into practice. Supported by an experienced facilitator you will be taken through a series of simulations and scenarios that you may encounter in your real life. Once you have worked through the simulations and scenarios you will then be provided with the tools and techniques necessary to resolve the issues.

All of our Medical Device courses are held at AMP Technology Centre, Sheffield, UK

Medical Device Regulatory Strategy

Date		Course Title	Duration	Price
January 2013	21	Introduction to Regulatory Strategies for Medical Devices	1 day	£600
	22-24	Regulatory Strategy – Practitioner Course	3 day	£1800
	25	Regulatory Strategy for Drug/Device and Borderline Medical Devices in Europe and the USA	1 day	£600
	24	Regulatory – EU Medical Device Regulations, The Upcoming Changes	1 day	£200
	30	Auditing Design Control for Medical Device Development Projects	1 day	£300
	31	Understanding the Requirements for Risk Management at the Pre-Clinical Phase of Development	1 day	£300

Medical Device Quality System Management

Date		Course Title	Duration	Price
February 2013	4	Introduction to QMS for Medical Devices	1 day	£600
	5-6	QMS – Practitioner Course	2 day	£1200
	7	Understanding the Difference between Pharma GMP and ISO 13485	1 day	£600
	8	Statistics in Medical Device Design, Quality Control and Quality Assurance	1 day	£600
	7	Human Factors for Medical Devices	1 day	£200
	27	Auditing the Technical File	1 day	£300
	28	Preparing a Regulatory Strategy for a Combination Product in Europe	1 day	£300

Medical Devices Clinical Investigation and Evaluation

Date		Course Title	Duration	Price
March 2013	11	Introduction to Clinical Evaluation for Medical Devices	1 day	£600
	12-13	Clinical Evaluation for Medical Devices – Practitioner Course	2 day	£1200
	14-15	Clinical Evaluation for Medical Devices – Advanced Course	2 day	£1200
	14	Understanding Medical Device Clinical Investigations in Europe	1 day	£200
	26	Developing a Quality Plan for your Organisation and your Product	1 day	£300
	27	Orthopaedic Risk Management – What You Should Know	1 day	£300

Medical Device Design Validation – Biological Pack

Date		Course Title	Duration	Price
April 2013	22	Introduction to Medical Device Design and Development	1 day	£600
	23-25	Medical Device Design Verification and Validation – Practitioner Course	3 day	£1800
	26	Software Validation for Medical Devices	1 day	£600
	25	Project Plans for Demonstrating Biocompatibility of High Risk Medical Devices	1 day	£200
	29	Auditing CAPA, Change, Risk Management and Validation as a System	1 day	£300
	30	Woundcare Risk Management – What You Should Know	1 day	£300

Key	Medical Device Course Series	Medical Device Study Day	Medical Device Workshop

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.

For more information contact the Medical Devices team at devices@nsf-dba.com, call +44 (0) 1709 331 031 or visit the website at www.nsf-dba.com

Forthcoming Courses

What's planned for December 2012 – March 2013

How to Audit – Chemical API

York Marriott Hotel, York, UK

11 December

The quality of any medicine depends on the quality of the Active Pharmaceutical Ingredient (API). We will show you what process 'critical control points' to focus on and what questions to ask about the systems and procedures that can have a direct impact on the purity, potency and stability of the API.

Course Fee: £495.00 plus VAT

How to Audit – Devices/Combination Products

York Marriott Hotel, York, UK

15 – 18 January

Determining the appropriate audit strategies when auditing a combination of drug/device and other combination products often leads to confusion as generally an emphasis is placed by the auditor onto their most 'comfortable' area of knowledge. This course aims to help you to develop the optimum strategy for your audit so that, regardless of regulation or technology, you focus upon the highest risk areas and deliver a robust summary as to the effectiveness of the lifecycle activities. We explore the regulations, risks and requirements in order to equip you with the best strategies and thought processes to deliver an objective, balanced and risk-based audit of your combination product.

Course Fee: £2400.00 plus VAT

Formulation & Processing (Part 1)

QP

Qualified Person & Professional Development Training

Hilton York Hotel, York, UK

21 – 25 January

First of a two-part module designed to provide pharmaceutical quality professionals with essential knowledge of formulation requirements and key processing methods (and critical control points) for the major pharmaceutical dosage forms.

Course Fee: £3200.00 plus VAT (First booking)
£2560.00 plus VAT (Additional bookings from same site)

How to Audit – QC Chemical Laboratories

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

30 – 31 January

The QC lab generates vitally important data used in troubleshooting, process improvements and product release. As an auditor you must challenge the systems and procedures that generate this data to ensure that it is accurate, reliable and traceable. We will show you how.

Course Fee: £1400.00 plus VAT

Pharmaceutical Packaging

QP

Qualified Person & Professional Development Training

York Marriott Hotel, York, UK

11 – 15 February

This course is designed to teach the aspiring QP, quality or technical professional all they need to know about packaging materials, regulations regarding labelling, the essential GMPs of packing operations and new initiatives regarding counterfeiting, etc. Includes a visit to a supplier of pharmaceutical packaging and labels.

Course Fee: £3200.00 plus VAT (First booking)
£2560.00 plus VAT (Additional bookings from same site)

GMP for Biological and Biotechnology Products

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

19 – 21 February

This course is designed for those with relatively little experience of applying GMP requirements to the manufacture of biologicals and biotech products. We will describe all the stages of biopharmaceuticals manufacture, from cell bank to finished product, and we will explain the key GMP and quality-critical issues for each and how to comply. If you are new to the biotech industry or a QP who has to take responsibility for this group of products, this course is for you.

Course Fee: £1800.00 plus VAT

How to Audit – Computer Systems

York Marriott Hotel, York, UK

20 – 21 February

Computers, and those operating them, have a profound impact on product safety, quality and efficacy. For most auditors what goes on inside these 'little black boxes' is bewildering. We will get down to the basics every auditor must consider when auditing computerised systems: what to look for and what questions to ask about inputs, outputs and what's happening inside the box itself!

Course Fee: £1400.00 plus VAT

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.

NSF DBA
The Health Sciences, Training, Consultancy and Auditing Experts
SM

Risk-Based Decision Making for Quality Professionals and QPs

Amsterdam Marriott Hotel, Amsterdam, The Netherlands

5 – 6 March

The toughest task facing any QP 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

Deviation and CAPA Systems – Best Practices

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

11 – 12 March

This focused course 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

Formulation & Processing (Part 2)

Qualified Person & Professional Development Training

Hilton York Hotel, York, UK

11 – 15 March

Second of a two-part module designed to provide pharmaceutical quality professionals with essential knowledge of formulation requirements and key processing methods (and critical control points) for the major pharmaceutical dosage forms.

Course Fee: £3200.00 plus VAT (First booking)
£2560.00 plus VAT (Additional bookings from same site)

Human Error Prevention

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

13 – 15 March

Human error is a commonly quoted cause of problems and deviations in our industry, but it is often not the real reason, just a convenient excuse, and so corrective actions such as 'retraining' are doomed to failure. You know that and so do the regulators! This unique course will help you to see beyond 'human error' as the root cause of problems. We will show you why people make mistakes and provide you with practical ways to reduce errors in the workplace.

Course Fee: £1800.00 plus VAT

Sterile Products Manufacture

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

25 – 28 March

One of our most popular courses. A comprehensive, four-day course on the latest EU and US GMP requirements for sterile products manufacture, plus practical advice on how to ensure compliance in a cost-effective and scientifically sound way.

Course Fee: £2400.00 plus VAT

Pharmaceutical Legislation Update: Continuing Professional Development for Qualified Persons & Technical Personnel

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

26 March

The Qualified Person and other Technical Personnel need to be informed and aware of pharmaceutical legislation. Changes in legislation and guidelines, and the interpretation of them, can have significant implications for the individual and their company. This is a one-day seminar that is designed to form part of your Continuing Professional Development.

Course Fee: £700.00 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

At Last!

New EU guidance on GMP for the manufacture of biopharmaceuticals and biotech products comes into force at the end of January 2013, but why did it take so long?

Bob Pietrowski takes a close look at the new annex.

A revised version of Annex 2 – GMP guidance for the manufacture of biopharmaceuticals – comes into effect on 31 January 2013. It replaces the original version of the Annex, which was published way back in the twentieth century. In that regard, it is among the last of the chapters and annexes of Volume 4 to be updated. Given the fact that biopharmaceuticals and biotech products represent not just the future but very much the present of human healthcare (7 of the top 10 best selling medicines worldwide are biopharmaceuticals), it is astonishing that the regulators have taken so long to provide essential guidance for this important group of products. And remember that it is not just manufacturers who benefit from clearer and more comprehensive guidance on GMP expectations; the annexes play an important part in ensuring that regulatory inspectors perform effective inspections which focus on the quality-critical aspects of production and control.

But rather than dwell upon the document's prolonged gestation period, let us welcome its arrival and take a close look at what has changed.

Overall Structure

The current version of Annex 2 is 5 pages long; the new version covers 30 pages, so there is clearly much more general and specific guidance to be found in the new version than in the old. Not only that, but the title of the annex is subtly different: it has changed from 'Manufacture of Biological Medicinal Products for Human Use' to 'Manufacture of Biological Active Substances and Medicinal Products for Human Use'. This makes it clear that the annex applies to API manufacture as well as the dosage form and, as such, spans both Part I and Part II of EudraLex Volume 4.

Furthermore, the structure of the new annex is radically different. The current version provides guidance under 8 major headings: Scope, Principle, Personnel, Premises and Equipment, Animal Quarters and Care, Documentation, Production and Quality Control. In the new version, the headings from Personnel to Quality Control are now contained in Part A of the Annex, titled 'General Guidance'. There is now a totally new section, Part B, 'Specific Guidance on Selected Product Types', which, as the title suggests, provides additional guidance on specific product types such as animal-sourced products, vaccines, recombinant DNA products, monoclonal antibodies, gene and cell therapy products and several more.

Finally, there is a useful glossary of terms for those who are not totally familiar with biological products and their unique vocabulary.

Guidance in Part A

As stated earlier, the guidance in Part A is much expanded over that found in the current annex. While the over-arching principles remain unchanged, more relevant and detailed guidance has been added (a good thing!) and some previous, dogmatic statements have been softened by encouragement to adopt the principles of Quality Risk Management to determine and justify working practices (a very good thing!). We don't have space here to review all the changes to the annex, so I will concentrate on those which I believe manufacturers should be particularly aware of.

Personnel

This section remains similar, but a key point of principle has been removed. Paragraph 2 of the current annex states, "Persons responsible for production and quality control should have an adequate background in relevant scientific disciplines… together with sufficient practical experience to enable them to exercise their management function for the process concerned". This has disappeared from the new version. Many may feel that such a paragraph is just 'motherhood and apple pie' and unnecessary, but biologicals are very different and I have personal experience of problems that can occur when such operations are managed by people without knowledge and experience of this special group of products!

Premises and Equipment

Previous statements regarding BCG vaccine, Bacillus anthracis, Clostridium botulinum, Clostridium tetani, etc, have been removed and quite right too! They were of no relevance to the vast majority of producers of biological products. I am a little surprised, however, that they were not transferred to the 'Vaccines' section of Part 2.

The section strongly emphasises the importance of environmental controls for open processes in order to prevent contamination. In this regard, the section references Annex 1 as a source of guidance for environmental control in areas where clean but not sterile processing is performed. While I applaud this clarification, I am a strong advocate of adopting an environmental classification system for biological processing that is not A, B, C and D, but rather borrows from ISO 14644 and the traditional pharmaceutical microbiological expectations to create a separate classification system (e.g. BIO1, BIO2, BIO3, etc) that is relevant to the products and processes. In my experience, such an approach has been accepted by both EU and FDA inspectors.

Animals

This section is now much longer, largely due to introductory text on how and where animals and animal tissue might be used in biologicals manufacture. The principles remain unchanged.

Documentation

Again, the principles remain unchanged, but there is extensive guidance for advanced therapy medicinal products and other cell or tissue based products.

Production

There is a new statement about the importance of Product Quality Reviews for both API and finished product, to confirm process robustness. This is to be welcomed.

Increased emphasis is placed on starting materials as a potential source of extraneous microbial, viral and prion contamination. Particular reference is made to media used for process simulations (broth fills).

There are large tracts of guidance specifically for products based upon human cells and tissue.

The subsection entitled 'Operating Principles' is much expanded (and not before time!). The new guidance covers:

- Change management
- Identification and validation of critical process steps
- Decontamination procedures, which should be qualified or validated depending upon which sentence of paragraph 55 you read!
- Enhanced guidance on removal and inactivation of viruses, etc
- Avoidance of release and cross-contamination for live products, including container integrity tests

Again, there are large tracts of text devoted to human cells and tissues.

Quality Control

While the basic principles are unchanged there are a number of important additions, including:

- Recommendation to perform stability studies on products prepared from intermediates which have been held for their maximum storage time (a very good proposal!)
- Guidance on QC and release strategies for products with a very short shelf life (similar in principle to guidance for radiopharmaceuticals)

Guidance Part B

This is specific guidance for specific product and will not be commented on here except to say that it is welcome. However, some sections are very thin – almost to the point of being unnecessary. It can also be argued that some of the detail in Part A regarding animal cell and tissue based products would perhaps have been better placed in Part B.

In Summary

Revised Annex 2 represents a major step forward in providing scientifically sound and rational GMP guidance for this very important group of healthcare products. It is such a shame that it took so long to arrive. It should not take 6 years to progress from a draft revision to the final version!

Perhaps it is time to allow industry to play a more active role in the preparation of such guidance. Such a move (which is embraced by ICH) would improve the knowledge and experience pool in the drafting committee and would perhaps provide the impetus to bring documents into force in a more timely manner.

The content of Annex 2 and many more issues will be discussed in our three-day training course 'GMP for Biological and Biotechnology Products' to be held in Manchester from 19 to 21 February 2013.

Mike Halliday, our QP Programme Manager, Reflects on New Beginnings…

Series 12 of the Qualified Person programme got under way with Module 1 on 'Pharmaceutical Law and Administration' scoring a fantastic average of 4.5 out of 5. The group of delegates included many new starters to the programme and represented a great start to the 2012/2013 academic year. One kind delegate even said the course was "simply the best I've ever attended". Many thanks, anon!

We have introduced a new evening of 'QP skills' and the first session was very well attended with great feedback. We will look forward to the next.

One thing is certain, the QP role is getting tougher and tougher and new initiatives and problems will keep the QP busy for years ahead. FMD, API declaration, excipient quality, risk-based everything, changes to the law and guidance, improving QMS, reliance on the audit programme…it's a tough world and the pharma industry is not getting off lightly.

At NSF-DBA we aim to provide the best possible training for this demanding role, certainly above the 'minimum' training stipulated. I for one would not be pleased to hear an airline pilot reassure his passengers that he had the 'minimum' training required! Nor should it be so for the QP who in one week could make decisions which impact on more patients than a pilot could fly in a lifetime.

I continue to be thoroughly impressed by the commitment, enthusiasm and dedication of the QP students on the course. Many have positioned their careers and negotiated over 10 years to get a place on the course and once there continue to be a credit to themselves and their companies! Looks like being a great, high achieving series ahead!

Formulation and Processing Part 1 and 2 are the first modules available in 2013. See pages 10 and 11 for details.

Introducing the New Director of Postgraduate Studies at the University of Strathclyde

NSF-DBA has worked with the University of Strathclyde for over 20 years and we have had the great pleasure of working with their extremely knowledgeable and professional staff. The team there has recently changed and we would like to introduce our new key contact.

"My name is Dr Chris Prior and I am Director of the Postgraduate Certificate, Diploma and MSc Degree courses in Pharmaceutical Quality and Good Manufacturing Practice at the University of Strathclyde.

I am a Neuropharmacologist and a Double-Graduate of the University of London. Currently, I am a Senior Lecturer within the Strathclyde Institute of Pharmacology and Biomedical Sciences. I am one of the longest serving contributors to the joint NSF-DBA/University of Strathclyde training programme, having been involved since 1998.

The courses are built around the joint NSF-DBA and the University of Strathclyde Qualified Persons training programme. Each module includes the study elements of the University of Strathclyde qualifications and the courses are then completed by a set of examinations managed by the University of Strathclyde. In addition, the MSc Degree course involves completion of a research project, usually conducted within the candidate's normal working environment.

The University of Strathclyde has its roots in an institution founded in the heart of Glasgow in 1794 by John Anderson as 'A Place of Useful Learning'. Today, it is Scotland's third largest University and it still lives by its founding creed as a place that excels in applied knowledge. It is a culturally diverse institution with an extremely strong international reputation."

NSF-DBA wishes Chris every success in his new role and looks forward to jointly supporting further University of Strathclyde and QP students.

If you are interested in becoming a QP or gaining one of our Postgraduate qualifications contact Stella Pearson-Smith at sps@nsf-dba.com

University of Strathclyde

QP Success

A first for us, one of NSF-DBA students – Leen van der Water of Pannoc, BV, has been awarded QP status from the Belgium regulatory authorities, based on her attendance on our modular based QP training. The training has long been popular with European delegates, it's great to see a European agency recognising its benefits too!

In addition we are very pleased to announce and congratulate the following UK QP students who have recently been awarded QP status:

- Jacqueline Barry, Scottish National Blood Transfusion Service
- David Franks, Reckitt Benckiser Healthcare (UK) Ltd
- Hazel Pitt, GE Healthcare Ltd

Calling all Responsible Pharmacists and Quality Professionals

Advanced Training and Development for Responsible Pharmacists, PIC/S Authorised Persons and Quality Professionals in Industry and in other Pharmaceutical Sectors in South Africa.

NSF-DBA is proud to announce its collaboration with one of Africa's leading academic institutions, the University of KwaZulu-Natal (UKZN) to bring South African Responsible Pharmacists, Authorised Persons (PIC/S) and other key Quality professionals the same advanced training that Qualified Persons undergo in the UK and EU.

The course that NSF-DBA will provide together with UKZN in South Africa is practical, face-to-face tuition. NSF-DBA are committed to improving the capabilities and responsibilities of South Africa's many Responsible Pharmacists and Quality Professionals. The schedule for 2013 courses is reflected in the table. All modules, except the practical module, will be presented at Glen Hove Conferencing, 52 Glenhove Road, in Johannesburg.

What NSF-DBA/UKZN Offer

- In-depth, face-to-face instruction from seasoned professionals
- UKZN University lecturers are acknowledged experts in their field
- All NSF-DBA tutors are eligible to act as QPs in the EU; many are current or former QP assessors and several are ex-UK medicines inspectors
- Students attending four or more of the modules will be assigned a personal tutor to provide advice and support throughout their training period
- As part of this over-arching effort to improve the skills of key professionals, NSF-DBA will also provide you with specialised managerial skills development seminars and ongoing support

Modules	2013 Dates
Active Pharmaceutical Ingredients	18-22 Feb
Analysis and Testing	18-22 Mar
Industrial Pharmacy Mathematics & Statistics	15-19 Apr
Investigational Medicinal Products	13-17 May
Pharmaceutical Formulation & Processing	10-14 Jun
Pharmaceutical Law and Administration	15-19 Jul
Pharmaceutical Packaging	12-16 Aug
Practical Module (to be held at UKZN)	16-20 Sep
Quality Management Systems and Good Manufacturing Practices	21-25 Oct
Roles & Professional Duties of a Responsible Pharmacist	11-15 Nov

For Further Information To find out more about entry requirements and module costs or for information about any specific module please contact: Allan Thomas by email at: **ajt@nsf-dba.com** or call: **+27 (0) 21 558 4515**

Sterile Products Training is a Huge Hit in Amsterdam

Twenty six delegates from eight different countries around the world attended our training course 'Sterile Products Manufacture' at the Park Hotel Amsterdam in October.

Along with courses such as 'Pharmaceutical GMP', 'Effective Pharmaceutical Audits and Self-Inspections' and 'Human Error Prevention', our sterile products training course is widely recognised as one of our flagship courses, unmatched by other training providers, and the delegate feedback certainly reflects this…

Our clients tell us that what sets our course apart from the rest is not just our ability to compare and contrast current EU and US GMP requirements for sterile products manufacture, but more importantly our ability to interpret the written guidance and provide practical recommendations on how to comply in a scientifically sound and cost-effective way, which allows you the opportunity to reduce costs whilst increasing product quality assurance.

A training course that saves you money? That doesn't happen every day!

> *"Great Course"*
> Linda Kjall, Fresenius-Kabi, Norway

> *"Great tutors! Buzz Group sessions are great!"*
> Lieke Hasper, Sanquin, The Netherlands

> *"I have taken a lot of knowledge out of this course and a lot of questions to ask my colleagues at work"*
> Ross Pouncey, Reckitt Benckiser Healthcare, UK

> *"Very good course. Very experienced and motivated tutors!"*
> Christina Steinbronn, Ferring GmbH, Germany

We will be holding 'Sterile Products Manufacture' again in Manchester from 25 to 28 March 2013. There is always great demand for places, so please book early to avoid disappointment.

NSF DBA
The Health Sciences, Training, Consultancy and Auditing Experts
SM

NSF-DBA People | Continuing to build our team in Europe

Steve Engels: Principal Consultant

We are delighted to announce that Steve Engels has joined us as a Principal Consultant, based in Switzerland.

Steve studied Pharmacy in South Africa before moving to Switzerland approximately 25 years ago. After several years with Roche, Steve joined Serono (now Merck Serono), where he spent over 20 years and held various senior positions in Quality Assurance and Manufacturing. In that time he conducted many GMP compliance audits around the world, co-ordinated Serono's corporate auditing activities and managed the company's Italian manufacturing facility in Bari for two years. Like all NSF-DBA people, he has a passion for training.

Steve speaks French, German and Italian as well as English and will play a key role in co-ordinating our consulting, auditing and training services in Switzerland, Germany, Austria, Italy and France.

If you would like to discuss how Steve and the Europe-based team can assist you by providing NSF-DBA's expert services in your own language, please contact him at **sengels@nsf-dba.com**

Martin Kloemkes: Consultant

Martin has a PhD in Biology/Biochemistry from the Technical University Aachen (Germany) and an MBA in General Management from SUNY, Albany/GSBA.

He is an experienced management professional with comprehensive knowledge and working experience in pharmaceutical R&D, R&D controlling, quality management, change management and Regulatory Affairs. He spent more than 25 years with Boehringer Ingelheim and J&J in various senior management positions, including Global Chem-Pharm Leader and Director of Regulatory Process Change Management.

Christof Langer: Consultant

With an Engineering Degree in Food and Biotechnology (MSc) from University of Applied Sciences, Vienna, Christof started his professional career at Baxter Inc.

Christof gained extensive, specialist experience in the fields of pharmaceutical manufacturing and quality throughout the entire supply chain of finished biologicals, plasma derived drugs, vaccines and recombinant products. His core expertise is in aseptic techniques as well as fill/finish and lyophilisation of sterile drugs.

As a Managing Director, he was responsible for successfully bringing a greenfield site into operation in the Czech Republic which was the world's first large scale cell-based vaccines facility with a BSL3 licence.

Christof is a trained Lean Six Sigma Black Belt, holds an MBA Degree in Executive Management and is a Risk Manager, certified by Quality, Austria.

Joining NSF-DBA, he brings expertise in consultancy, auditing and training in the GxP environment of big pharma as well as biotech.

Marie-Cécile Krief: Consultant

Marie-Cécile is a PhD Pharmacist by profession with a Masters Degree in Quality Control of Medicines. She has more than 20 years' experience in the pharmaceutical industry as a Qualified Person and GMP senior auditor in Europe. She has broad experience, particularly with quality control laboratories, quality management and active pharmaceutical ingredients.

Marie-Cécile has worked as a senior GxP compliance auditor in the area of APIs, excipients and packaging materials for drug products manufacturers and cosmetic manufacturers. She has delivered training in relevant subjects in quality operations and is recognised for auditor training according to GMP, GDP and cosmetics guidelines.

She is a member of the Société Française des Sciences et Techniques Pharmaceutiques (Sfstp) and the Association pour les Produits Propres et Stériles (A3P).

Rob Stephenson: Consultant

Rob has over 30 years' experience in the manufacturing sector of Pharmaceutical and Personal Care products working for companies including Boots, Lilly, Unilever, Coty and Pfizer. He has broad knowledge and experience in Quality Management and Training and more recently in the compliant implementation and operation of a wide range of Laboratory and Business Systems.

As a long-standing member of the GAMP® Europe Steering Committee Rob has contributed material to GAMP®5 and the Good Practice Guide on "A Risk-Based Approach to Operation of GxP Computerised Systems" for which he was co-leader.

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