DBA

The Journal of David Begg Associates

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Annex 1
Manufacture of Sterile Medicinal Products

EU GMPs
Tougher now than the US?

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An NSF International Company

welcome

Listening and Responding to your Needs

Bob Pietrowski, Managing Partner David Begg Associates

We regularly talk to our clients and ask them how we can improve our services, and lately we've been receiving the same two responses:

- We are inundated with mailings and emails from you! Can't you do something about it?
- You are really good at what you do and we would love to use you, but money is tight right now. Can you do anything to reduce your prices?

The answer to each question is the same – yes!

Mailings and emailings

An unfortunate consequence of increasing the number of courses we run, which we do because you ask us to, is that we have more course brochures to send out. We love trees as much as you and we have been concerned for some time about the volume of paper we send out.

After summer, we promise not to send you more than one letter each month.

As for emails, you may have noticed that the regular course emails have now been replaced by a regular e-Newsletter. We hope you appreciate the change.

Our fees

We understand that in the current economic climate, money for training and consultancy is limited. That is why we have decided to reduce our prices in response to your requests. Please see the back page of this Journal to find out more.

We are determined to provide the quality of service you need at a price you can afford without intruding into your busy lives.

Please let us know if there is more we can do.

Bob Pietrowski
Managing Partner

DBA The Pharmaceutical Training Specialists

Tech Talk

Bob Pietrowski argues that EU GMP requirements are now the most demanding on the planet!

Goodbye to Fear, Doubt & Anxiety

Hello to Extreme Uncertainty?

Ten years ago, there was a general belief in the global pharmaceutical industry that US GMPs were the most stringent in the world and, thus, if you could satisfy FDA expectations, you could satisfy anyone. At that time most major companies focused their efforts on achieving strict compliance with FDA expectations to avoid the strict penalties seen for non-compliance.

Ten years on, the situation has – in our view – completely changed. Now, the written EU GMPs are the most comprehensive and demanding on the planet and their interpretation by EU regulatory inspectors – especially those from the UK and Ireland – are the most difficult to satisfy!

Such a statement demands justification. Let us then look at areas of pharmaceutical GMP where EU expectations exceed those of the FDA…

- Clinical Trials Manufacture
- Sterile Products Manufacture
- Quality Management Systems
- Risk Management
- Product Quality Review
- Raw Material Control
- Computerised Systems
- Biopharmaceuticals Manufacture
- Batch Release and the Role of the QP

Clinical Trials Manufacture

The adoption of European directive 2001/20/EC, subsequent modification of the GMP directive and revision of Annex 13 have led to the EU now having by far the most stringent GMP requirements for the manufacture and control of clinical supplies (investigational medicinal products). Moreover, these GMP expectations are enforced by EU regulatory agencies via inspection.

By contrast, the FDA's guidance for the manufacture of clinical supplies, Guideline on the Preparation of Investigational New Drug Products (Human and Animal) of 1991, is much less detailed and, perhaps surprisingly, the FDA does not routinely inspect manufacturers to ensure compliance. The FDA's approach to clinical trials was exemplified in January 2006 when they proposed that Phase I studies be made exempt from the requirement to comply with cGMP – a move which was resisted both by industry and the US public.

This lack of enforcement of GMP for the manufacture of clinical supplies by the FDA has resulted in several traumatic experiences for US manufacturers when inspected by EU regulators!

Tech Talk

Sterile Products Manufacture

EU's latest version of Annex 1 cements the region's GMP requirements as the most stringent for the manufacture of sterile products. In particular, the requirements for monitoring of 5 micron particles, new requirements for environmental protection of capping operations, the zoning of manufacturing areas and changing requirements, and the control of steam sterilisation processes are far more demanding than current US requirements, where detailed guidance refers only to aseptically prepared products.

In short, if you are in compliance with Annex 1, you will meet global GMP expectations for sterile products, but if you comply only with US expectations, you will **not** satisfy EU requirements.

Quality Management Systems

EU GMP inspectors have long placed greater emphasis on the quality management system than have the FDA, even after the US introduced the system's approach to inspections. Indeed, EU inspectors have also for many years included and sampled all parts of the quality management system during each inspection. It is common for US companies to be cited by European inspectors for failure to implement and operate an effective quality management system, based upon Quality Assurance principles.

The adoption of ICH Q10 and the proposed entry of the FDA into PIC/S may go some way to further harmonisation of expectations, but change is unlikely to be instantaneous.

Risk Management

It can be argued that the FDA embraced risk management far earlier than did the EU; it featured strongly in the FDA's cGMPs for the 21st century initiative and the agency formally endorsed ICH Q9 much sooner than the EU.

Many European regulators will counter this argument by stating that risk management has always been an implicit part of EU GMP requirements and so there was not a similar need to emphasise the topic. For example, EU inspectors have always classified their inspection observations according to risk.

Risk management is now explicit in Chapter 1 of the EU GMP Guide and ICH Q9 has been adopted as Annex 20. Perhaps most importantly, risk assessments (and in particular **formal** risk assessment) are demanded in numerous sections of the EU GMP Guide and its Annexes. Additionally, it is becoming increasingly common for European pharmaceutical companies to be required to provide formal risk assessments to their regulatory agencies in support of changes to the Manufacturing Authorisation (e.g. modification of facilities, introduction of new products, etc). We are not aware of similar demands by the FDA.

Raw Material Control

EU's expectations for the control of raw materials, detailed in Annex 8 of the GMP Guide, are far more stringent than those of the FDA, especially in terms of requirements for assurance of identity and the development of risk-based, statistical sampling plans as opposed to the "blanket" application of $\sqrt{n}+1$. When we audit a US company with no prior experience of EU GMP requirements, this is an audit observation we can write on the plane before we arrive!

The EU is currently proposing a revision of certain parts of the GMPs (e.g. Chapter 5) covering raw materials controls and supplier assurance that may make this area even more stringent.

Computerised Systems

It was the FDA back in 1983, through people such as Ron Tetzlaff, who first raised the genuine issue of the increasing application of computerised systems to pharmaceutical manufacture and control and the need to ensure that such systems are compliant with the principles of GMP. Only later was attention turned to the records created by such systems and the use of electronic signatures. 21 CFR Part 11 served to provide a structural framework to regulate these activities. Unfortunately, as is so often the case, the whole issue of computerised systems and electronic records and signatures took on a life and momentum of its own and soon grew beyond what was initially envisaged.

By comparison, the EU's Annex 11 on computerised systems was an example of restraint and common sense, enabling the user to apply key principles with care and intelligence. Whenever I have introduced US IT specialists to Annex 11, their response has been very positive.

Over the years, the FDA has worked with industry to agree an interpretation of GMP requirements for computerised systems which is pragmatic and achievable. However, here in Europe there have been moves to substantially "beef up" the guidance in Annex 11. These moves – driven, it must be said, more by industry than regulators – have resulted in the latest draft "revision" of Annex 11. I say "revision" because the new draft is a complete re-write. There is now more detail in Annex 11 and there is widespread concern that some of the new proposals, especially regarding electronic documents, data and record retention, may be subject to misinterpretation and over enthusiastic application, so making EU requirements more rigorous than those agreed by the FDA and US industry.

Biopharmaceuticals Manufacture

The proposed revision of Annex 2, Manufacture of Biological Medicinal Products for Human Use, was reviewed in detail in the last issue of the DBA Journal. In that, we described the document as "well intentioned but flawed".

Since then, some industry groups – especially those associated with the development of ICH Q7a – have questioned the need for such an Annex at all, given the adoption of Q7a as Part 2 of EudraLex Volume 4. Personally, I don't support this view. The

scope of ICH Q7a is largely limited to products manufactured by large scale fermentation, so excluding many newer biological products, and the guidance to be found in Chapter 18 lacks depth and detail. There is a clear need to provide pragmatic guidance to those entering the biologicals manufacturing industry for the first time and who lack the "history" and understanding of key GMP requirements, which have grown up as a result of incidents in the past. As the wise man said, "If you ignore history, you are destined to repeat history".

However, having made a case for the existence of Annex 2, I believe that there are key sections of it, particularly in its reference to Annex 1 and environmental expectations for sterile products, which are open to misinterpretation and unnecessary over-specification.

By contrast, the FDA's regulatory guidance for biologics and biotech products is far less detailed or onerous, being based predominantly on ICH Q7a, an ageing inspection guideline and a few sections of 21 CF Parts 600-680 for traditional biologics.

Batch Release and the Role of the QP

The regulations and arrangements surrounding batch release in the EU are without doubt the most rigorous in the world. No batch of licensed or investigational medicinal product may be released for sale or supply until it has been certified by a QP – a uniquely European position – and the educational and practical experience criteria for the QP are defined in law, surpassing any similar expectations anywhere else on the planet. Furthermore, the criteria for batch review and assessment are detailed in the EU GMP Guide (Annex 16) and, again, exceed any similar guidance internationally.

By contrast, the FDA has set no similar formal requirements of the batch release process or batch release personnel. These processes are defined in company procedures only and it is these procedures which are reviewed by the FDA for compliance with 21 CFR requirements regarding the role of the Quality Control Unit and that products which fail to meet their approved quality specifications will be rejected.

Moreover, the duties of the European QP are becoming more and more onerous, whilst their powers of discretion are a continuing subject of debate.

So why has the situation changed?

We believe that this dramatic turnaround in relative GMP requirements is due to a series of events.

Events in the USA

It became clear in the final years of the 20th century that the FDA had neither the personnel nor other resources to continue to regulate the global pharmaceutical industry in its traditional way. Out of this realisation came the agency's 21st century GMP initiative, which sought to balance regulatory oversight with patient risk. Thus, the FDA became more pragmatic in its expectations, more open to different ways of thinking and more outward looking.

Efforts to achieve Mutual Recognition between USA and EU

The now seemingly doomed attempt to have a Mutual Recognition Agreement between USA and the EU on GMP standards so that inspection of the other's industry could be rendered unnecessary, undoubtedly provided impetus for the development of new GMP regulations and expectations in the EU so that "equivalence" of standards could be achieved. Thus, we had the implementation of regulation and guidance on topics traditionally regarded as FDA requirements, such as…

- Product quality review
- Regulation of API manufacture
- Ongoing stability testing

However, in adding these "American" requirements to EU GMP expectations, additional criteria and demands were frequently added, so increasing the overall level of stringency.

Impact of ICH

The success of industry/regulatory initiatives through ICH, which have brought us Q8, 9, 10 and (soon) 11, has brought about a greater harmonisation of international agreement on key quality and GMP principles, so narrowing the gap between EU and FDA expectations. However, in some areas, EU has been more earnest in applying these expectations.

Continuing Expansion of the EU

The EU has expanded rapidly in recent years – from 15 member states to 27. The arrival of new countries into the regulated environment of pharmaceuticals has posed challenges to politicians and regulators as they seek to develop, adopt and communicate GMP and other requirements to an increasing number of countries with an increasingly variable history of regulation and GMP compliance. It should be of no surprise to anyone, therefore, that the expansion of the Union has coincided with an increased level of activity concerning GMP regulation and guidance.

Implications for Global Manufacturers

The swing in GMP stringency from the FDA to the EU has clear implications for any pharmaceutical manufacturer; when preparing global quality standards and GMP requirements, look first at EU GMP regulations and guidelines, not those of the FDA. The days when manufacturers could content themselves with the knowledge that they are in compliance with FDA requirements and so they can satisfy the requirements of all international markets are long gone – as several US based companies have discovered to their cost in recent years.

Perhaps it's time to say goodbye to Fear, Doubt & Anxiety and instead bid a reluctant hello to Extreme Uncertainty!

Tech Talk 2

Annex 1, Manufacture of Sterile Medicinal Products

So, at last we have it! On 14 February 2008, the European Commission finally published the latest version of Annex 1.

There were no real surprises in the document, as many of the changes were either previewed in the previous draft or had been widely leaked in advance, but compliance with some of the changes will challenge manufacturers of sterile products, especially those outside the EU.

The major changes to the previous version of Annex 1 centre on five key areas:

- Requirements for classification of clean rooms and clean air devices
- Monitoring of clean rooms and clean air devices
- Guidance for media simulations
- Bioburden monitoring
- Capping of freeze-dried vials

All the proposed changes must be adopted by manufacturers by 1 March 2009, with the exception of the last and probably most controversial change – that to environmental control of capping of freeze-dried vials – which must be implemented by 1 March 2010.

Classification of Clean Rooms and Clean Air Devices

As widely anticipated, the requirements for the maximum permissible number of particles of 5 microns or larger per cubic metre of air in Grade A and Grade B environments have been revised to bring them (almost!) in line with ISO 14644-1 expectations. The ISO standard proposes a maximum of 29 particles per cubic metre for ISO 5 environments. This figure has been adopted in Annex 1 for Grade B areas at rest and requirements for other Grades are revised accordingly. However, for some reason, the maximum permissible number of 5 micron particles or larger per cubic metre of air in Grade A environments is 20, equivalent to ISO 4.8. Why there should be a lower figure for 5 micron particles between Grade A and Grade B at rest, when the requirements for 0.5 micron particles and larger are the same, is difficult to understand!

Table 1 summarises the revised expectations for particles and for microbiological contamination.

The Annex requires that sample volumes of at least one cubic metre be used to classify clean rooms and clean air devices to the revised standards.

Monitoring of Clean Rooms and Clean Air Devices

In the main, requirements for monitoring of clean rooms and clean air devices remain unchanged in principle, but two key areas of clarification have been added…

- Whilst it is necessary to sample at least one cubic metre of air at each sample location to demonstrate compliance with the particulate requirements for Grade A during *classification*, it is **not** necessary to take 1 m³ samples during *monitoring* of Grade A zones.

- The previous proposed revision to Annex 1, published in September 2005, proposed continuous particulate monitoring of Grade A environments and recommended it for Grade B areas. In the new document there is no such requirement or recommendation. However, the Annex states *"The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded."* In practice, it is difficult to envisage how this could be accomplished without continuous particle counting.

Guidance on Acceptance Criteria for Media Simulations

New guidance on acceptance criteria for media simulations (broth fills) appears in the new version of the Annex. Any reference to a contamination level of less than one in one thousand containers with 95% confidence has gone and the new requirements are as follows…

- The target should be zero growth
- When filling fewer than 5000 units:
  - ➢ no contamination

Table 1: Revised Environmental Expectations for Clean Rooms

GRADE	AT REST**		IN OPERATION					
	Particles		Particles		Microbiological Contamination***			
	Maximum permitted number of particles per m³ equal to or above		Maximum permitted number of particles per m³ equal to or above		air sample cfu/m³	settle plates (dia 90mm) cfu/4h	contact plates (dia 55mm) cfu/plate	glove print 5 fingers cfu/glove
	0.5μ	5μ	0.5μ	5μ				
A*	3520	20	3520	20	<1	<1	<1	<1
B	3520	29	352 000	2900	10	5	5	5
C	352 000	2900	3520 000	29 000	100	50	25	-
D	3520 000	29 000	not defined	not defined	200	100	50	-

* normally a unidirectional air flow zone

** to be restored after a short 'clean up' period of 15-20 minutes

*** these are average values

- When filling 5000 to 10000 units:
  - ➢ 1 contaminated unit requires investigation and consideration of a repeat media fill
  - ➢ 2 contaminated units are cause for revalidation, following investigation
- When filling more than 10000 units:
  - ➢ 1 contaminated unit requires investigation (but not necessarily consideration of a repeat media fill)
  - ➢ 2 contaminated units are, as before, cause for revalidation, following investigation

Importantly, and wisely, the document also states that intermittent incidents of contamination should be investigated as they may be indicative of low-level, ongoing contamination associated with the process.

Bioburden Monitoring

The previous version of Annex 1 stated *"The bioburden should be monitored before sterilisation."* This implied a requirement to carry out bioburden testing of all batches of aseptic and terminally sterilised products, although the wording was not so explicit.

The revised Annex retains the wording quoted above, but goes on to specify that a bioburden assay should be performed on each batch of aseptically filled product and terminally sterilised product, but where overkill sterilisation parameters are set for terminally sterilised products, bioburden may be monitored only at scheduled intervals instead of every batch. There is a clear requirement to perform bioburden testing of every batch of terminally sterilised product which is subject to parametric release.

Capping of Freeze-Dried Vials

The EU has long had concerns about the microbiological integrity of vials prior to capping and some EU regulatory authorities, particularly the British, have for many years demanded additional environmental protection for stoppered but uncapped vials.

These concerns have resulted in a significant new requirement for the handling of capping operations which will require many manufacturers to re-engineer their clean rooms, involving significant cost and downtime.

The EU authorities clearly recognise this and have given manufacturers an extra year to comply with the new guidance – full compliance is required by 1 March 2010!

Annex 1 states the following…

118 *The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion.*

119 *The equipment used to crimp vials can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction.*

120 *Vial capping can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with Grade A air supply until the cap has been crimped.*

121 *Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimise microbial contamination.*

122 *Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.*

So what does this mean in practice?

- Capping operations must be protected to avoid contamination
- Grade A air must be supplied to all areas where uncapped vials are stored, transferred and processed
- Whilst it may not be possible to demonstrate compliance with the particulate requirements of Grade A during the capping operation, compliance with the microbiological requirements is expected
- The environmental cleanliness of the background room (and the clothing regime for operators) will be determined by the security of environmental protection provided to the vials and the degree of operator intrusion into the critical zone
- It may not be necessary to sterilise the aluminium overseals before use, but it would be wise to monitor the microbiological contamination of shipments from suppliers

In Summary

The revised Annex 1 contains some welcome practical improvements to the previous version…

- The relaxation of 5 micron particulate requirements to come into line with ISO 14644-1 standards
- The expectation that 1 m^3 air samples will be used for particulate classification, but not monitoring, of Grade A zones
- The revised acceptance criteria for media fills
- The relaxation of bioburden testing requirements for products sterilised using an overkill cycle

However, some of the new requirements are less easy to welcome…

- The requirements for ISO 4.8 particulate standards in Grade A rather than ISO 5
- The stringent requirements for capping of vials in the absence of data to demonstrate that currently adopted practices are microbiologically insecure

All these issues and more will be discussed in detail in our training course "A Practical Interpretation of Annex 1", to be held in Manchester on 23 June, and again in our course "Sterile Products Manufacture", to be held in Dublin in September.

Forthcoming Courses

What's planned for the next five months, June – October 2008

Key Topics in Sterile Products Manufacture:

A Practical Interpretation of Annex 1

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

23 June 2008

A short course designed to bring you up to date with the latest requirements of Annex 1 of the EU GMP Guide and, more importantly, how to comply in a practical, cost-effective way.

Course Fee: £675.00 plus VAT

Environmental Monitoring for Sterile Products Manufacture

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

24 & 25 June 2008

This course is designed to help you to understand the methodologies of environmental monitoring, how to use them to design a comprehensive, targeted monitoring programme and how to act upon the results to assure real control.

Course Fee: £1280.00 plus VAT

Process Simulations

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

26 June 2008

A short course designed to ensure that your process simulations (broth fills) comply with current EU and US requirements. We will also tell you how to deal with problems arising from process simulations.

Course Fee: £675.00 plus VAT

Pharmaceutical GMP

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

15 - 18 September 2008

Europe's most popular GMP course! An excellent overview of EU and US GMP regulations, plus up to the minute guidance on current "hot topics".

Course Fee: £2210.00 plus VAT

Sterile Products Manufacture

Clontarf Castle Hotel, Dublin, Ireland

22 - 25 September 2008

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: £2310.00

GMP Requirements for Biologics and Biotech Products

San Juan Marriott Resort & Stellaris Casino, San Juan, Puerto Rico

23 - 25 September 2008

This three day course will provide attendees with up to the minute information on GMP requirements for biologics and biotech manufacture, along with current industry best practice. The course will include a practical interpretation of EU's draft revision of GMP guidance for these products.

Course Fee: $2625.00

GMP for Clinical Trials Manufacture and Supply

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

29 September - 2 October 2008

Essential training in current EU and US GMP regulations for the manufacture, testing, importation and distribution of clinical supplies. As last year, we have a European regulatory inspector to give a keynote talk on GMP expectations and current regulatory trends.

Course Fee: £2210.00 plus VAT

Book online at www.DBA-global.com

DBA The Pharmaceutical Training Specialists

GMP Requirements for Biologics and Biotech Products

Hilton Boston Financial District, Boston, Massachusetts

30 September - 2 October 2008

This three day course will provide attendees with up to the minute information on GMP requirements for biologics and biotech manufacture, along with current industry best practice. The course will include a practical interpretation of EU's draft revision of GMP guidance for these products.

Course Fee: $2625.00

Pharmaceutical Law and Administration

NEW SERIES

Qualified Person & Professional Development Training

York Marriott Hotel, York, UK

6 - 10 October 2008

All the prospective QP or pharmaceutical professional needs to know about EU, UK and US pharmaceutical legislation and regulatory bodies. This course provides the depth of knowledge and understanding you really need to act in a professional capacity in a highly regulated industry.

Course Fee: £3105.00 plus VAT

Qualified Person & Professional Development Training

FREE SEMINAR

York Marriott Hotel, York, UK

7 October 2008

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.

Sponsor Seminar

Qualified Person & Professional Development Training

FREE SEMINAR

York Marriott Hotel, York, UK

8 October 2008

Are you currently acting as a sponsor for someone undergoing QP training or are you likely to be in the future? This free seminar, hosted by DBA and including presentations from the Royal Pharmaceutical Society of Great Britain, the Royal Society for Chemistry and the Institute of Biology, is designed to help you to understand the professional and ethical responsibilities that go with the sponsor role so that you can better fulfil your duties and better support your trainee QPs.

Good Documentation Practices

Hilton Hotel, Manchester, UK

7 & 8 October 2008

This course is essential for anyone wishing to make their documentation system more efficient, cost-effective, user-friendly and compliant with EU and US GMP requirements. The course will be highly participative – you will design key documents and perfect your document writing skills.

Course Fee: £1280.00 plus VAT

Annex 11 and Electronic Documents

NEW COURSE

Hilton Hotel, Manchester, UK

9 October 2008

EU are proposing to totally re-write their guidance on GMP requirements for computerised systems (Annex 11). Come and learn what is proposed and how it will impact on key areas of operation such as electronic documentation and records retention.

Course Fee: £675.00 plus VAT

Making the Transition from GAMP4 to GAMP5

NEW COURSE

Hilton Hotel, Manchester, UK

10 October 2008

GAMP4 has been replaced by GAMP5. This one day course will explain the key differences between the old and new guidance and what you will need to do to make the transition to compliance with GAMP5.

Course Fee: £675.00 plus VAT

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

Call us on: +44 (0) 1751 432999 or email: courses@DBA-global.com

Forthcoming Courses

What's planned for the next five months, June – October 2008

Applying ICH Q10 Pharmaceutical Quality System

NEW COURSE

Manchester Airport Marriott Hotel, Manchester, UK
7 & 8 October 2008

Learn how to apply the latest ICH guidance to your Quality Management System and stay ahead of impending US and EU requirements.

Course Fee: £1280.00 plus VAT

A Practical Application of GMP for API and Excipient Suppliers and their Customers

Maryborough Hotel & Spa, Cork, Ireland
13 - 16 October 2008

This comprehensive course is designed both for manufacturers of APIs and excipients, and also those who purchase them for dosage form manufacture. We will teach you the key GMP requirements to be satisfied, how to achieve compliance and how to audit and assess the competency and GMP compliance status of suppliers. Includes a visit to a modern API manufacturing site.

Course Fee: £2310.00

Product Quality Reviews

Manchester Airport Marriott Hotel, Manchester, UK
14 October 2008

Chapter 1 of the EU GMP guide now includes a requirement to carry out periodic reviews of all licensed medicinal products. This course will provide you with clear guidance on how to design and perform quality reviews which are efficient, cost-effective and value-adding.

Course Fee: £675.00 plus VAT

Pharmaceutical Legislation Update

Continuing Professional Development for Qualified Persons & Technical Personnel

Manchester Airport Marriott Hotel, Manchester, UK
15 October 2008

Your annual top-up!

Current and proposed changes to EU and US legislation and GMP requirements and their impact on QPs and technical managers.

Course Fee: £675.00 plus VAT

Pharmaceutical GMP

Hilton Singapore Hotel, Singapore
21 - 23 October 2008

Europe's most popular GMP course now available to Singapore and Pacific Rim companies. An excellent overview of EU and US GMP regulations, plus up to the minute guidance on current "hot topics".

Course Fee: S$4000.00

Good Autoclave Practice

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
21 - 23 October 2008

A comprehensive course on the practicalities of autoclave selection, qualification, cycle design and validation, ongoing performance monitoring and management. You will learn current regulatory expectations for steam sterilisation, how to qualify and validate autoclaves effectively, how to troubleshoot problems and best industry practice for monitoring and management of autoclaves.

Course Fee: £2210.00 plus VAT

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

Call us on +44 (0) 1751 432999 or email: courses@DBA-global.com

Book online at www.DBA-global.com

In-House Training

The Most Effective Way to Develop and Improve Your Team

They say if you want to develop an individual, send them on a training course, but if you want to develop and motivate a whole team, bring the training course in-house.

DBA has been providing high quality training on all aspects of pharmaceutical GMP and quality management for over 22 years now. You will be well aware of the range of training courses that we offer publicly, but you may not be so aware that in a typical year we run close to 100 in-house courses in as many as 16 different countries across the globe; training around 1800 people.

Gerry Migliaccio
Pfizer, USA

"The results surpassed our expectations. The QA leaders who participated in the training now have much greater confidence in their decision making ability. DBA provided training that could be immediately used in their daily activities."

Ever since DBA started we have conducted training 'in-house', so we have a great deal of experience in working with companies to produce tailored programmes to meet their specific needs. This can range from a single day of training up to a suite of linked four day modules delivered over several years. As long as you have a minimum of ten people who require the training then we can work with you to design a course, or range of courses, to fit your requirements.

A satisfied customer recently said to us "With DBA`s help we were able to tailor a GMP course for our organisation using traditional GMPs as the foundation and intelligently applying them to our novel production process".

The thing that we believe distinguishes us from other training providers is our ability to offer a full service. By this we mean that we will respond to your initial enquiry immediately (our SOP says within 24 hours!); we will always speak with you to gain a clear understanding of your needs, the sort of products you have, the backgrounds of the people to be trained, etc, and then we will produce a draft programme, send this to you as a formal proposal and continue to work with you to refine the content to ensure that the course really meets your precise needs. Once we have delivered the training we don't just walk away. We view this as the start of a relationship between you and DBA, so we are happy for you to contact us at any time after the course for help and advice for which, providing that we can supply this over the phone or by email, we do not charge. It is all part of the DBA service!

Obviously, when a company asks us to design and deliver training for them they will have a specific goal in mind. This can range from simply needing to fill a knowledge gap in a particular section of their organisation to wanting to change the company's culture by educating a group of employees so that they become 'change agents'. We judge our success by the same criteria in each case – has our training made a positive contribution to the organisation? Have we added value?

David Baird, Manager, Analytical Services Department, at BOC Medical said of the training we provided "The internal courses that DBA ran for us were excellent. It was particularly pleasing the way they customised them to our business making them much more relevant and increasing the power of the learning points. I am intending to use them again in the very near future".

We have the greatest opportunity to make a substantive change within an organisation when they ask us to deliver structured, modular training across a period of time. Here we can draw upon our 20+ years' experience of training Qualified Persons in Europe. In delivering this sort of modular training we try to achieve two objectives; firstly, we aim to provide delegates with the technical knowledge they need to make the right 'science' based business decisions and, secondly, we help delegates to develop a wide range of interpersonal and decision making skills in order to allow them to successfully implement change and business improvement with minimal disruption.

Mark King
Actavis
UK Ltd

"What you get with using DBA for internal training is an opportunity to get up close and personal with recognised industry experts who have a passion for sharing knowledge and experience. By understanding our specific requirements and how we operate as a business, the training was tailor made to suit our needs. The value in our organisation has come in not only delivering the theory in a very clear and interesting format, but in providing people with the challenge and skills to think for themselves. What I also value hugely is that the service doesn't end on the last day of the training course or the day that the invoice is paid. By establishing these close relationships my experience is that the DBA team are only too happy to help in answering questions for many years to come."

After we ran such a two year programme for Pfizer in the USA, Gerry Migliaccio, the Vice President of Global Quality, was extremely pleased with the results – his specific comments are highlighted on the left.

We know that in difficult times such as these, training is often the first item on the budget to go, but now is the ideal time to prepare your staff for the coming upturn, and with our new pricing structure, announced elsewhere in this journal, in-house training with us represents excellent value for money.

So if you have the need for authoritative, tailored in-house training on any aspect of pharmaceutical quality please just give us a call and we will be only too happy to work with you.

Industry News

EU News

EU Anti-counterfeiting Proposals

In March 2008 the Commission launched a public consultation on ideas for amending the regulatory framework governing the manufacture, trading and distribution of active substances and medicines for human use. The Commission is proposing the following new measures to combat counterfeiting:

- **Subjecting all parties in the distribution chain to pharmaceutical legislation**
- **Improving product integrity and traceability**
- **Sharpening the technical requirements for GMP and GDP**
- **Tightening inspections and supervision**
- **Improving transparency**

The Commission is also considering making audits of GMP/GDP compliance by qualified auditors (these might include third-party audits by accredited companies) mandatory. This would apply not only to dealings between manufacturers and contract manufacturers but to the relationship between manufacturers and supplying/purchasing wholesalers, where there were grounds for suspicion of non-compliance. The Commission says that "acceptance of third-party audits by accredited companies could be considered".

Ideas for improving product integrity include requiring a unique seal for the outer packaging of a medicinal product in its journey from the manufacturer to the retailer or wholesaler. The right to open the seal would be restricted to the market authorisation holder and the end-user of the product (i.e. hospital, healthcare professional, patient). This rule would not apply to all medicines but to certain categories of product identified through a risk-based approach, taking into account the potential public health impact of counterfeiting and the profit strategies of counterfeiters. The move would be backed up by a ban on repackaging.

In terms of traceability, the consultation document suggests introducing an obligatory product pedigree, comprising a "unique and centrally accessible record of all past ownerships and transactions". The supplied retailer/pharmacy would be the final traceable point in the distribution chain.

EU Reflection Paper on Water for Injection (WFI) by RO

In March 2008 the EMEA issued a "Reflection Paper" on WFI by RO. Exactly why the EMEA wants to stimulate this discussion at this time is unclear. There does not appear to be a ground swell of opinion among users or suppliers to lobby for a change in the regulations to allow the use of membranes to manufacture WFI, such as there was in the 1990s. Rather, with the progression to hot water sanitisable systems there is probably a trend the other way and some companies are considering using distillation to make both WFI and Purified Water, particularly where the Purified Water volume requirement is relatively low compared with the WFI usage. Putting in a new Purified Water generation and distribution system is now around the same cost as putting in a new WFI generation and distribution system, not because the product quality requirement has changed but because the expectations of inspectors and industry approaches have changed.

All aspects of quality and regulatory requirements for WFI will be discussed in detail in our training course "Sterile Products Manufacture" to be held in Dublin in September.

EU Implementation of ICH Q9

A new section on Quality Risk Management is to be added to Chapter 1 of Part I of the EU GMP Guide, which will become effective from 1 July 2008. This new section adds the statement that "Quality Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively".

It also adds the two primary principles from ICH Q9 but adds the words "experience with the process" to the first principle, as shown below:

- **The evaluation of the risk to quality should be based on scientific knowledge, experience with the process and ultimately link to the protection of the patient; and**
- **The level of effort, formality and documentation of the Quality Risk Management process should be commensurate with the level of risk**

The section ends by referring to the new Annex 20, which contains the full text of ICH Q9, and which became effective on 1 March 2008.

In April 2008 the Commission also published a proposed revision of Part II of the EU GMP Guide (on APIs). This revision is proposed to incorporate principles of Quality Risk Management as laid down in the ICH guideline Q9, which corresponds to similar changes made to Part I Chapter 1 of the Guide. The new section on Quality Risk Management is proposed to be introduced as Section 2.2. The remaining sections of Chapter 2 are consequently renumbered. No other changes have been proposed.

Revision to Chapter 4: Documentation

A proposed revision to Chapter 4 was published on 11 April 2008. The main reason for the revision is to accommodate the changes relating to electronic documentation, to coincide with the revision of Annex 11 on Computer Systems (see later). However, there have been extensive additional changes to the "Principle" and "General" sections to provide additional detail.

Comments on this proposal should be sent to the Commission by 31 October 2008.

The potential impact of this proposal forms a key part of our new course "Annex 11 and Electronic Documents" to be held in Manchester in October.

Annex 11: Computerised Systems

A proposed revision to Annex 11 was published on 11 April 2008. This is a total re-write and significant expansion of this Annex.

Already MHRA inspectors have expressed concerns with the wording proposed, particularly around Section 15 (Back up, Migration, Archiving, Retrieval), where they believe there is a danger of over interpretation by both regulators and industry that could result in another "Part 11" situation. This has the potential to become a major issue, particularly where modern Process Analytical Technology (PAT) applications are collecting large amounts of data.

Our new course "Annex 11 and Electronic Documents" will discuss these concerns in detail.

Annex 13: Investigational Medicinal Products (IMPs)

In April 2008 the Commission published a draft revision of Annex 13 for comment.

The following changes are proposed:

- A minor change has been made to Section 3 in order to reinforce the principle of independence between production and quality control functions in cases where the number of personnel involved is small
- Changes are proposed to Sections 36 and 37 to supplement, for IMPs, the guidance for reference and retention samples given in Annex 19
- Section 44 has been reworded to enhance understanding of the two-step release procedure that applies to IMPs. This proposes that there should be a change control process for the Product Specification File that is defined in a Technical Agreement between the Qualified Person and the Sponsor

Comments are due by 31 October 2008.

These proposed changes will be discussed during our course "GMP for Clinical Trials Manufacture and Supply" to be held in Manchester in September

ICH News

ICH Q11: Active Pharmaceutical Ingredients (API) Development

A Concept Paper for a new ICH guideline to focus on development of APIs has been approved by the Steering Committee. A new expert working group will start drafting the guideline, to be designated Q11, at the ICH meeting in June 2008.

The Q11 guideline will aim to define the development process for APIs similar to those contained in Q8 for medicinal products; just as Q8 gave detail on the requirements for the 3.2.P.2 Section of the CTD, Q11 will give the detail for the 3.2.S.2 Section.

QP Issues

Series 10 of our Qualified Person & Professional Development Training Starts in October

Our tenth series of Qualified Person & Professional Development Training starts in York on 6 October with the first module, Pharmaceutical Law and Administration.

Interest in this tenth series has been fantastic so far, but there are still places available – both for the whole series and individual modules – so if you would like to book a place or receive more information, please contact Stella Pearson-Smith on +44 (0)1751 432999 or at qp@DBA-global.com

Second Meeting of the David Begg Associates / University of Strathclyde QP Alumni Association

Following the great success of the inaugural meeting last year, the second meeting of the QP Alumni Association will take place at the York Marriott on Thursday 10 and Friday 11 July. For further details, please contact Stella Pearson-Smith as above.

Congratulations to:
In the past four months, DBA has helped the following people obtain QP status:

Stephen Davenport – SSL International
Ronnie O'Connell – Cobra Biomanufacturing plc
Dru Homer – Genzyme Ireland Ltd

New DBA People

Neil Wilkinson joins as a Partner

We are delighted to announce that Neil Wilkinson joined us as a Partner in mid-June

Neil joined us from AstraZeneca, where he was Senior Director of Global Quality.

A chemist by training, Neil has spent his entire career to date with what is now AstraZeneca. In that time he held roles in QC, QA, Production, Supplier Assurance and International Manufacturing/Compliance. During the late 1990s, Neil lived and worked in the USA, where he became involved with PhRMA (the US research-based industry association). On his return to the UK he became actively involved in the equivalent European association, EFPIA. Until recently he was chair of EFPIA's Manufacturing and GMP ad-hoc group and was EFPIA topic leader on the ICH Q10 (Pharmaceutical Quality System) Expert Working Group – a task he hoped to conclude before joining us. Neil is also an active member of both ISPE and PDA.

Outside work, Neil is a keen sports fan, a lifelong supporter of Manchester United, and a bit of a "petrol head" – he has a passion for cars and motor racing. To keep fit he enjoys cycling and walking – something he intends to do more of when he moves to North Yorkshire. Neil has two teenage sons living with their mother in Cheshire. His partner Janeen is currently relocating from Belgium to Kent, along with her cats and dogs. Overall, then, weekends are a major logistical exercise!

Neil's arrival significantly strengthens the DBA Partner team and allows us to improve the quality and breadth of service that we provide to you.

Welcome to DBA-global.com

Five years since introducing our original website, we have taken the decision to not only update it with a brand new look, but to re-launch the site under the new name of DBA-global.com.

The new logo and colour scheme featured on the website works across all our marketing communications to present a fresher, more contemporary feel to DBA. But it's not just about image; we've worked hard with our web development team to improve both the functionality and usability of the site.

We have strived to make the site more user friendly with new links leading to the relevant areas of the site making it easier for users, both old and new, to gather information about DBA, our courses and giving them the opportunity to book courses online.

Naturally, the security of the site and protection of our clients' personal data has always been of the top priority to us and we hope more clients will feel confident in booking courses online. A complete training calendar is featured on the site so you can plan for all your annual training activity at the click of a mouse.

The forum on the new website is now bigger and better than before and we hope that this new interactive forum will encourage conversations between our clients, our Partners and Consultants. Contact details for all of our trainers are featured on the site and we are keen that clients get in touch with any questions about our internal or external training programmes.

DBA-global.com is regularly updated and features a News section running stories about both DBA and topical industry news stories from the pharmaceutical profession. And to help you keep abreast of industry news you can download any issue of the DBA Journal or our latest e-newsletter.

Managing Partner, Bob Pietrowski, said "We are delighted to be launching the new DBA website, the easy access to and navigation around the site will really benefit our clients. We hope that DBA-global.com will encourage more people to explore what DBA has to offer and to become involved with this exciting, new online pharmaceutical community."

To explore our new website, visit www.DBA-global.com. We would value your feedback on the new site so why not register on the Forum and give us your thoughts?

The Pharmaceutical Training Specialists

Responding to the Current Economic Climate and your Reduced Budgets

Whenever we talk to our clients about the quality of service we provide, we get the same answers:

- The quality of our work is second to none
- We are more expensive than our competitors and so sometimes our clients have to use other consultants when they would prefer to use us

I know that I speak for all of my colleagues when I say we joined DBA because we wanted to give something back to an industry that had been very good to us over the years. If some clients can't afford to use us for all their needs, then we are failing them – and we are failing ourselves.

You will be aware that late last year we were acquired by NSF International. What you may not know is that NSF is a not-for-profit organisation. This means that we put provision of service above pursuit of profit. This has allowed us to review our business model and make some immediate changes to our charges in order to make it easier for you to justify using our services.

For example:

- If you want us to train ten of your staff at your premises, our fee will be at least 13% lower than a year ago
- If you require us to come to you and provide three days of consultancy (and you are based outside the UK), our fee will be around 11% lower than this time last year

Money is tight for you at the moment and it is only right that we should respond to this fact by making significant changes.

One thing definitely will not change, however, and that is the quality of our service to you.

We realise that, even with these changes, we are still not the cheapest, but you wouldn't expect us to be. We believe, however, that we represent excellent value for money.

Why not contact us and ask us to quote for your next project – we think you will be very pleasantly surprised!

In the next DBA Journal

Industry News: As ever, we search for regulatory changes so you don't have to; Tech Talk: ICH Q10, Pharmaceutical Quality Systems; Location, Location, Location…: New venues for 2009; DBA People: We welcome another new face to the team; Forthcoming Courses: A review of our training courses for Winter 2008/9.

If you have any comments or suggestions for the next issue of the Journal, please email us at journal@DBA-global.com

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