DBA

The Journal of David Begg Associates

Issue 10 Autumn 2008

US Office opens in Boston

Meet the US team

ICH Q10

An opportunity for us all

An NSF International Company

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welcome

Bob Pietrowski, Managing Partner David Begg Associates

David Begg Associates USA

October 2008 represents an important point in the development of David Begg Associates – we open our first office in the USA.

More details about the Boston office, our US Partner Jim Morris and our growing team of consultants can be found on pages 6 and 7 of this Journal. We are very excited about this as it at last allows us to serve our US customers from a local base and, for the first time, enables us to offer our European customers FDA-related consultancy and audits from experienced US Industry professionals.

GMP – Too much of a good thing!

My article in the last Journal on why EU GMP expectations are now the toughest in the world drew numerous emails from readers – most notably from readers in the US who felt that I was criticising the FDA and US GMP standards!

Let me be perfectly clear. I draw absolutely no pride from my belief that EU GMP requirements are tougher than those of FDA – far from it. I believe that Regulators all over the world, but particularly in parts of the EU, are in danger of pursuing higher levels of GMP for GMP's sake, and not for the benefit of the patient. Recent initiatives through ICH represent a welcome attempt to bring everyone's attention back to what is really important.

Just because GMP requirements are getting tougher, it doesn't mean that they are getting better or that patients are being better protected.

Bob Pietrowski
Managing Partner

DBA The Pharmaceutical Training Specialists

Tech talk

ICH Q10

'An opportunity for us all'

The ICH Q10 Guideline 'Pharmaceutical Quality System' was signed off as a Step 4 document at the ICH meeting in Portland, Oregon, in June 2008.

The Q10 Guideline will now be introduced into the regulatory systems of FDA, EMEA and Japan over the next few months and its subsequent implementation phase will be highly influential in shaping how modern quality management approaches evolve and develop within the Pharmaceutical Industry.

DBA's Neil Wilkinson was the EU Industry topic leader within the ICH Q10 Expert Work Group and was an active participant in the Q10 journey – from the early conceptual discussions with FDA around the need to modernise the Pharmaceutical Industry and associated regulatory procedures, to the ICH 'Q' discussions leading to the agreed ICH Quality Vision and the subsequent Guidelines Q8, Q9 and Q10 (and now Q11) needed to deliver it, through to the writing of the Q10 document.

If you have not yet reviewed the content of the ICH Q10 Guideline and considered its impact upon how your company operates its Quality System, then it makes good business sense for you to do this soon.

It is critical that Q10 should not just be looked at as a Quality Guideline, relevant only to the 'Quality Folks' in a company. It should be seen as an essential key business system that drives good business performance and improvement.

But what about that old Pharmaceutical Industry argument – 'we are a heavily regulated Industry and have our own GMPs'?

Well, this article will attempt to convince you that this is not valid – to improve the performance of the Pharmaceutical Industry and to facilitate more science and risk-based regulatory approaches something new was needed – enter ICH Q10.

Background – the Need to Change

The Pharmaceutical Industry is currently facing significant challenges both in the external economic environment in which we operate and internally with the need to modernise and make pharmaceutical manufacturing more efficient.

To continue to operate with a focus on 'blind compliance' leading to inefficient ways of working is no longer an option.

External pressure from governments seeking reductions in the costs of healthcare spending, including the cost of drugs, and a sustained slow down in the introduction of new drugs from the R&D based Industry are significant challenges we face as an Industry.

Additionally, internally, the Pharmaceutical Industry is well behind other Industries in terms of manufacturing understanding and efficiency, Quality Management and continual improvement approaches. It was recognised, in part, that regulatory agency processes have played their part in the situation by making changes and improvements difficult to make – however Industry did also help drive itself into a mindset of 'blind compliance' during the late 1990s/early 2000s. Studies published by PricewaterhouseCoopers and IBM concluded that pharmaceutical manufacturing was highly inefficient, operating 2.5 sigma processes with a heavy emphasis on inspection and QC to provide suitable products to the market place.

Wall Street Journal 2003

"The Pharmaceutical Industry has a little secret: Even as it invents new drugs its manufacturing techniques lag far behind those of potato chip and laundry soap makers."

So – there were, and still are, strong drivers for change. It was clear that the current regulatory processes and GMPs required significant overhaul and a culture change to facilitate the changes required.

The 'Quality Journey'

The FDA's 'cGMP for the 21st Century' initiative in the early 2000s led the way and catalysed the subsequent development of the ICH Quality Vision in 2003 that then led to the ICH Guidelines ICH Q8/Q8R (Pharmaceutical Development), ICH Q9 (Quality Risk Management) and ICH Q10 (Pharmaceutical Quality System).

Additionally, more recently, Q11 (Development and Manufacture of Drug Substances) and revisions to the variations and post-approval changes regulations in the EU and US are also now actively being progressed – so we are still on the journey.

Note that all the above Guidelines are strongly inter-related, with Q10 providing the 'umbrella' Pharmaceutical Quality System (PQS) to sit above and glue it all together.

The Key Messages on Q10

Remember – Q10 is heavily inter-related with Q8, Q9 (and now Q11).

It has the full endorsement of the regulators as being an acceptable approach to satisfying expectations for a modern Pharmaceutical Quality System. In the eyes of the Regulators – having a Quality System is mandatory, having a Q10 PQS is 'strongly recommended'. The use of alternates will have to be justified.

In order to learn from approaches to Quality Management used in other Industries, Q10 takes the framework of ISO 9001 – and adds a pharmaceutical context. So what are the major aspects to consider in Q10?

Aim of Q10

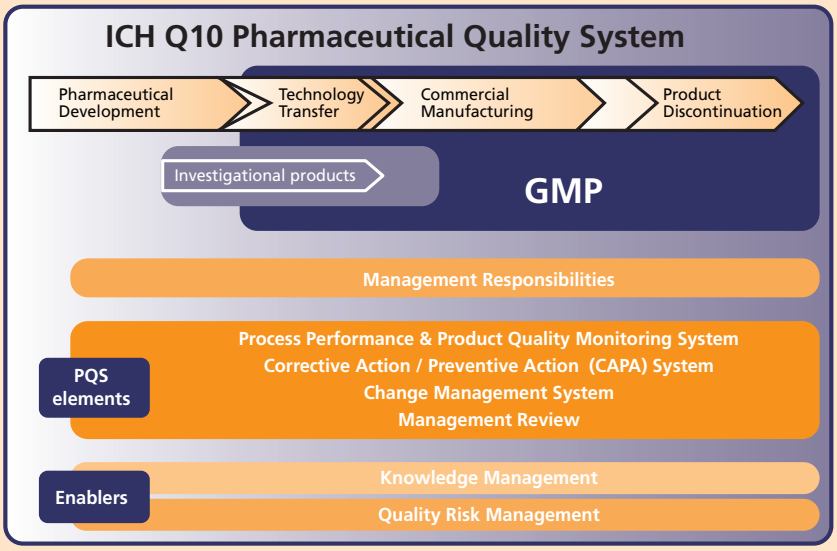
Its aim is to promote a 'paradigm shift' away from just applying GMP at discrete stages of the product lifecycle, to having a comprehensive Quality System approach 'over the lifecycle' of the product. A Q10 PQS will therefore link together the different stages of the product lifecycle and strengthen links between development and manufacturing organisations, including the highly important management of and use of product knowledge.

Scope

Q10 is applicable to the development and manufacture of drug substances (API) **and** drug products, **including** biotechnology and biological products through the product lifecycle – so it goes beyond the GMPs. **Good Manufacturing Practice is the necessary but not sufficient condition for Good Manufacturing Performance.**

Annex 2

Diagram of the ICH Q10 Pharamaceutical Quality System Model



It is important to apply Q10 in a manner that is **appropriate and proportionate to the stages of the lifecycle**, so not to inhibit innovation and improvements. Q10 is applied as a system, and can accommodate **both new and existing products**.

Regulatory Approaches

The intent of Q10 is that regulatory approaches for a specific product or site should be commensurate with:

- The level of product and process understanding
- The use and results of Quality Risk Management
- The effectiveness of the PQS

The types of opportunities that this may bring are listed in Q10 Annex 1.

Annex 1 – Potential Opportunities to Enhance Science and Risk-Based Regulatory Approaches*

*Note: This annex reflects potential opportunities to enhance regulatory approaches. The actual regulatory process will be determined by region.

- Scenario and Potential Opportunity
  1. *Comply with GMPs*
     - ➢ Compliance – status quo
  2. *Demonstrate effective Pharmaceutical Quality System, including effective use of Quality Risk Management principles (e.g. ICH Q9 and ICH Q10)*
     - ➢ Opportunity to:
       - ✦ Increase use of risk-based approaches for regulatory inspections

3. *Demonstrate product and process understanding, including effective use of Quality Risk Management principles (e.g. ICH Q8 and ICH Q9)*
   - ➢ Opportunity to:
     - ✦ Facilitate science-based pharmaceutical quality assessment
     - ✦ Enable innovative approaches to process validation
     - ✦ Establish real-time release mechanisms
4. *Demonstrate effective Pharmaceutical Quality System and product and process understanding, including the use of Quality Risk Management principles (ICH Q8, ICH Q9 and ICH Q10)*
   - ➢ Opportunity to:
     - ✦ Increase use of risk-based approaches for regulatory inspections
     - ✦ Facilitate science-based pharmaceutical quality assessment
     - ✦ Optimise science and risk-based post-approval change processes to maximise benefits from innovation and continual improvement
     - ✦ Enable innovative approaches to process validation
     - ✦ Establish real-time release mechanisms

As a result, a more science and risk-based regulatory oversight should result.

So, there is agreement in principle between Regulators and Industry to this. How this will evolve during implementation remains to be seen – however it is very much up to companies to propose and have dialogue with the Regulators as things move forward. We are in a position of both Regulators and Industry having to go through a big learning phase during the implementation of Q10 and related ICH Guidelines.

To be successful, we will have to work together, develop trust – and **both** parties overcome internal conservation, whilst removing some of the 'traditional' silo thinking by working across functional boundaries in organisations (e.g. Review and Inspection, Development, Operations, Regulatory).

Continual Improvement

Q10 seeks to facilitate a culture of continual improvement. This will mean moving the Industry forward, both organisationally and technically.

Q10 re-enforces a number of very key areas seen within the ISO 9001 approach, and partly in the GMPs. These include:

- Management responsibility
- Monitoring of product quality and process performance
- Corrective and Preventive Action (CAPA)
- Change management
- Management reviews

To undertake this successfully, the effective use of Quality Risk Management and Knowledge Management need to be embedded/integrated throughout the product lifecycle.

So where could Q10 take us?

A successful implementation of ICH Q10, alongside ICH Q8/Q9, should help move pharmaceutical development and manufacturing and associated regulatory processes towards a much more science and risk-based way of operating. This approach should be consistent across the ICH region and also where observer countries/regions 'sign up' to the principles.

This all sounds highly desirable, but does it make business sense?

Well, in addition to the above thinking there are seen to be significant business benefits available, which are a perfect fit with today's initiatives driving towards operational excellence, using Six-Sigma and/or lean thinking.

These include:

- Improved understanding and performance of manufacturing and business processes
- Reductions in the cost of internal failures (rejects, reworks, reprocessing, investigation costs, etc.) and costs of Quality
- Reductions in the costs of holding duplicate stock and operating multiple processes as changes/improvements are more easily made with less 'prior-approval' changes
- Reductions in the costs and delays of certain regulatory submissions
- Improved relationships between Industry and Regulators focused on science and risk management, allowing Industry and Regulators to focus on the things that matter – not just on 'blind compliance'
- Risk-based regulatory scrutiny – commensurate with a firm's use of ICH Q8/Q9/Q10

So Q10 presents a great opportunity to contribute to modernising and improving the approach to Quality Management within the Pharmaceutical Industry, giving us the opportunity to improve the efficiency and effectiveness of our Industry and better facilitate improvement and innovation.

DBA offers a two day course on ICH Q10 (to be held in San Juan, Puerto Rico, from 22 to 23 January 2009, in Philadelphia, USA, from 26 to 27 January 2009 and in San Francisco, USA, from 29 to 30 January 2009) and a three day course on Preparing for the Future: Successful Implementation of ICH Q8, 9 and 10 (to be held in London, UK, from 2 to 4 June 2009 and in Philadelphia, USA, from 18 to 20 August 2009). Both courses can be run internally at your company.

opens an office in the USA

David Begg Associates has always been fortunate to have a healthy customer base in North America – last year around 12% of our business came from USA and Canada and this year the percentage will be significantly larger.

That is why we have set up a US company – David Begg Associates USA LLC – to serve our growing customer base in North America and also to allow us to offer auditing, consultancy and training from experienced US Industry professionals to our customers all over the world. DBA-USA officially opened for business on 1 October.

DBA-USA has its offices in downtown Boston, from which we will serve clients throughout North America, although if all goes to plan we will eventually open a West Coast office.

Having a US base will allow us to provide services locally and, importantly, charge in US dollars rather than sterling. That does not mean, however, that we will not continue to provide our North American clients with European consultants with EU GMP experience where that is what the company needs. Rather, we are well placed to provide a truly global service.

So far, we have a US Partner, Jim Morris, and two additional consultants, Karen Migliaccio and Glenn Sutker. Their backgrounds are detailed on the next page. We are committed to adding to this very strong base and are actively looking to recruit further consultants.

If you are interested in learning how DBA-USA can assist you, why not contact us at

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Our US Team

With extensive industrial experience ranging from Research & Development to commercial manufacture and from tablets and capsules to bulk biologics and biotechnology products, our US team has the breadth of experience and depth of knowledge to provide our clients worldwide with industry-leading training and pragmatic solutions to your quality management, cGMP and regulatory compliance issues.

Jim Morris BA Biol, MBA
Partner

Jim has significant experience in plant operations in the US and Europe. He has held positions as Deputy Director QA/QC and Regulatory Affairs at MassBiologics, Director of QA/QC for the Biologics business unit of Cilag AG and a number of Quality Assurance and Manufacturing roles with Pfizer over a 16 year time frame, culminating as the head of Quality Assurance for Pfizer in Latina, Italy.

His particular area of interest and expertise is parenteral production but Jim has worked with a broad range of dosage forms including human, veterinary and consumer products

Karen Migliaccio BS MS Analytical Chemistry

Karen is an analytical chemist and has over 27 years' experience in the Pharmaceutical Industry. She worked for Pfizer, Inc. in a series of progressively more responsible positions in Quality Assurance and Control functions. She has worked in technical, supervisory and management positions in both commercial and R&D quality functions. Most recently, Karen held the position of Senior Director, Quality Operations, at Pfizer's Groton, CT R&D site.

Karen has extensive knowledge of GMP requirements, regulatory inspections, and Quality Systems development and implementation. She has a working knowledge of the drug development process, regulatory filing, and product launch. She has provided Quality oversight for diverse manufacturing processes, including API, drug product intermediates, clinical supplies manufacturing and packaging, and a variety of drug product formulations.

Glenn Sutker BS MS Analytical Chemistry

A chemist with a Masters degree in analytical chemistry from Rensselaer Polytechnic Institute, Glenn retired from Pfizer, Inc. after nearly 35 years of service in Global Manufacturing Quality Operations.

At Pfizer, Glenn served in a number of capacities of increasing responsibility at both a Manufacturing Site and Center. During his career, among other roles, he was Laboratory Manager, Quality Assurance Manager, Site Quality Operations Director, Area Leader/Senior Director/Vice President of Quality Operations for Europe, Ireland/Singapore, and the Americas. In his last position he was Vice President Quality Operations Center and was responsible for leading the QO site support, Global Manufacturing Compliance and Global Quality Analytical Resources (laboratory) units.

Forthcoming Courses

What's planned for the next four months, November 2008 – February 2009

How to Simplify and Improve Your Change Management System

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
4-6 November 2008

The control of planned and unplanned changes is perhaps the greatest challenge facing any pharmaceutical company and its quality management staff. This highly popular 3 day course will provide you with practical guidance on how to simplify your change control systems to make them quick and efficient, whilst at the same time ensuring compliance with regulatory expectations.

Course Fee: £1690.00 plus VAT

Pharmaceutical Packaging GMP – Compliance at the Operational Level

Clontarf Castle Hotel, Dublin, Ireland
4-6 November 2008

Key EU and US GMP requirements for pharmaceutical packing operations, including up to the minute developments in security systems and ISO GMP expectations for primary packaging components.

Course Fee: £1790.00

Quality Aspects of the CTD

Hilton York Hotel, York, UK
17-20 November 2008

Run in conjunction with Regulatory Resources Group, this course is designed to provide you with a clear understanding of the technical data requirements for EU and US registration submissions and the implications for subsequent commercial manufacture.

Course Fee: £2210.00 plus VAT

A-Z of Pharmaceutical Water Systems

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
17-20 November 2008

This 4 day course will provide you with the latest information on EU and US regulatory expectations for water systems and practical advice on system design, validation, monitoring and management, as well as troubleshooting and risk assessment. In short, all you will ever need to know about water systems!

Course Fee: £2210.00 plus VAT

Medicinal Chemistry & Therapeutics

Qualified Person & Professional Development Training
York Marriott Hotel, York, UK
17-21 November 2008

All the prospective Qualified Person or pharmaceutical professional needs to know about how drugs act on the body, the major therapeutic classes of drugs and how they should be handled in manufacturing.

Course Fee: £3105.00 plus VAT

Human Error: Causes and Prevention

Crowne Plaza Hotel, Philadelphia Center City, USA
18-20 November 2008

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 this 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: $2625.00

Pharmaceutical Legislation Update

Continuing Professional Development for Qualified Persons & Technical Personnel
Radisson SAS Hotel, Dublin Airport, Dublin, Ireland
2 December 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. Includes a keynote talk from the Irish Medicines Board.

Course Fee: £725.00

EU GMP Requirements for the Manufacture of Sterile Products

Philadelphia Marriott Downtown, Philadelphia, USA
2-4 December 2008

This 3 day course will explain EU GMP expectations for the manufacture and control of sterile products, show how they differ from current FDA expectations, and provide you with practical advice on how to comply in a scientifically sound and cost-effective way.

Course Fee: $2625.00

Book online at www.DBA-global.com

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DBA
The Pharmaceutical Training Specialists

Pharmaceutical GMP

Amsterdam Marriott Hotel, Amsterdam, The Netherlands
15-18 December 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: £2310.00

Formulation & Processing (Part 1)

Qualified Person & Professional Development Training
Hilton York Hotel, York, UK
19-23 January 2009
First of a two part module designed to provide the prospective Qualified Person or pharmaceutical professional with essential knowledge of formulation requirements and key processing methods for the major classes of pharmaceutical dosage forms.
Course Fee: £3105.00 plus VAT

Sterile Products Manufacture

Hilton Singapore Hotel, Singapore
20-22 January 2009
One of our most popular courses. A comprehensive 3 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: S$4000.00

Applying ICH Q10: Pharmaceutical Quality System

San Juan Marriott Resort & Stellaris Casino, San Juan, Puerto Rico
22-23 January 2009

Crowne Plaza Hotel, Philadelphia Center City, USA
26-27 January 2009

San Francisco Marriott Fisherman's Wharf, San Francisco, USA
29-30 January 2009
Learn how to apply the latest and most influential ICH guidance to your Quality Management System from someone who wrote it! Helping you to stay ahead of impending US and EU requirements.
Course Fee: $1775.00

Risk-Based Decision Making in Sterile Products Manufacture

Amsterdam Marriott Hotel, Amsterdam, The Netherlands
26-29 January 2009
How to use modern risk management techniques to take sound, science-based decisions on the types of incidents which can and do occur during the manufacture of sterile products.
Course Fee: £2310.00

Essential Elements of Good Control Laboratory Practice

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
26-27 January 2009
Current EU and US GMP expectations for Quality Control laboratories. An essential overview.
Course Fee: £1280.00 plus VAT

Investigating Out of Specification Results

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
28 January 2009
Practical advice on how to develop, implement and operate procedures and practices which will meet the latest US and EU regulatory requirements for identifying, investigating and acting on out of specification (OOS) and out of trend (OOT) results.
Course Fee: £675.00 plus VAT

Ongoing Stability Testing

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
29 January 2009
The best available advice on how to design, implement, operate and manage systems and procedures for ongoing stability testing plus essential information on how to analyse data to determine shelf life.
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 432 999 or email: courses@DBA-global.com

Forthcoming Courses

What's planned for the next five months, November 2008 -February 2009

Electronic Documentation and Annex 11

NEW COURSE

London Marriott Hotel Kensington, London, UK
3 February 2009

EU Regulators are totally re-writing 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

GMP for IT Specialists

NEW COURSE

London Marriott Hotel Kensington, London, UK
4 February 2009

Clear, practical advice for IT specialists on how to ensure that your practices and procedures comply with the latest EU and US GMP requirements.

Course Fee: £675.00 plus VAT

How to Maintain the Validated State of Computerised Systems

NEW COURSE

London Marriott Hotel Kensington, London, UK
5 February 2009

Validating computerised systems to current EU and US expectations is one thing – maintaining the validated status amid constant changes to hardware, software, operating procedures, regulatory expectations, etc, is quite another! We will provide you with sound advice on how to succeed.

Course Fee: £675.00 plus VAT

Satisfying EU GMP Requirements for Sterile Products Manufacture

San Francisco Marriott Fisherman's Wharf, San Francisco, USA
10-12 February 2009

This 3 day course will explain EU GMP expectations for the manufacture and control of sterile products, show how they differ from current FDA expectations, and provide you with practical advice on how to comply in a scientifically sound and cost-effective way.

Course Fee: $2675.00

Risk-Based Decision Making for Quality Professionals and QPs

NEW COURSE

London Marriott Hotel, Kensington, London, UK
10-11 February 2009

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

Course Fee: £1280.00 plus VAT

GMP for Biological and Biotechnology Products

NEW COURSE

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
17-19 February 2009

This 3 day course is designed for people 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 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: £1690.00 plus VAT

Cleaning Validation

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
24-25 February 2009

This ever-popular course will provide you with what you need to be able to design, execute and audit cleaning validation studies to current EU and US expectations. There will be Industry case studies on validation experiences for APIs, biotech products and solid dosage forms.

Course Fee: £1280.00 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@DBA-global.com

Book online at www.DBA-global.com

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Training courses for 2009

September saw the launch of our 2009 training programmes – one for the UK and Europe and the other for USA and North America.

The number of courses we now offer in the USA has grown significantly over the last year to the point where they warrant their own programme for the very first time. This was launched at the September PDA/FDA Joint Conference in Washington DC and has since been mailed to all our clients in North America.

So now the European Training Programme is devoted exclusively to our courses in UK and Europe. We have added some important new titles to all the old favourites and we are confident that you will like what we have to offer, just as you have in previous years.

We also know that times are tight for you right now – budgets have been cut and one of the first casualties of restraint is always training, closely followed by travel! That is why we have decided to keep our training prices for 2009 the same as for 2008 – in today's climate that represents a price fall in real terms!

If you haven't received a copy of our 2009 training programme and would like one, please contact us at our Kirkbymoorside, UK, or Boston, USA, office and we will send one to you. Alternatively, you can download the programme in pdf form from our website.

New DBA People

George Urwin joins as an Associate Consultant

A chemist by training, George has over 30 years of pharmaceutical experience which covers a broad range of product types – from tablets and capsules to sterile biotech products – as well as active pharmaceutical ingredient manufacture.

Before joining David Begg Associates, George was Head of Quality for Sanofi-Aventis in the UK. Prior to that, he held senior Quality Management positions with a range of international pharmaceutical companies including Novartis in Switzerland, where he was Deputy to the Head of Corporate Quality, Shire Pharmaceuticals in the UK, where he was Director of International QA, and Lonza, where he was Head of Corporate Quality.

From his wide experience, George has an excellent knowledge of international GMP requirements and of quality management systems and we are confident that his arrival will further enhance the service we provide to you.

George has the misfortune to be a supporter of Newcastle United Football Club, but he doesn't let this spoil his natural optimism and good humour.

Industry News

EU News

Compilation of Community Procedures on Inspection (CoCP)

A new section entitled 'A Model for Risk-Based Planning for Inspections of Pharmaceutical Manufacturers' became effective in April 2008

The introduction to this new section states that "Competent Authorities of the Member States need to develop a systematic and risk-based approach to make the best use of their surveillance and enforcement resources while maximising the impact of those resources on the public health".

The principle of this document is that planning and scheduling of inspections are realised as follows:

- Compile all relevant sites/facilities in a list
- Establish risk ranking (based on product risk and compliance factor) for each site
- Establish the necessary expenditure of inspection time for each site
- Establish the inspection frequency
- Prioritise inspections by calculating individual inspection dates per site
- Establish risk ranking

There is a section on 'Inspection Duration'. This contains a large table that gives guidance values for the required inspection time per type of site. The type of manufacturing site is classified by the relevant dosage form and the manufacturing process. The risk ranking assumes that critical processes and products would have a higher public health consequence than less critical ones.

The next section covers 'Inspection Frequency'. This states that large companies may be inspected department by department, a full general GMP inspection being completed at least every five years. Generally the interval between inspections should not exceed three years. Low risk companies meeting GMP do not need inspecting as often as those making high risk products or with greater GMP deficiencies.

Annex 3: Radiopharmaceuticals

After publication of a draft revision of Annex 3 on Manufacture of Radiopharmaceuticals in September 2006 the final version of the revised Annex was published on 1 September 2008 and becomes effective on 1 March 2009.

Guidance is given as to the GMP and non-GMP parts of the process. For example, Cyclotron and Reactor steps are regarded as non-GMP, with GMP coming into force as soon as the chemical synthesis starts.

The revision to the Annex provides guidance for some relatively new technology, in particular Positron Emission Tomography (PET). This process often involves very short lived radionuclides and these present a challenge to the normal release processes for medicinal products. Some of these radionuclides have a shelf life of hours and therefore the active ingredient is synthesised, made into a dosage form and administered, in less than one working day.

For sterile products, the Qualified Person release is still required, but there will be at least a two stage process – releasing the product for administration and finally releasing the product after sterility testing.

Parametric release is (still) seen as necessary, as are systems to follow up in the event of failed result when all testing has been completed.

Briefly the principal changes from the previous version of Annex 3 are:

- New sections on Introduction, QA and Documentation and a glossary
- Risk assessment is strongly emphasised
- The guideline applies to materials for use in clinical trials
- GMP requirements for the API are given, in line with EU GMP Part II (ICH Q7a)
- There are new requirements on environmental control during manufacture, which are confusing and poorly written. In particular, Section 25 states that the requirements of Annex 1 should be followed, but Section 27 then appears to suggest that for closed (aseptic?) processes, Grade C would be acceptable, although for aseptic (open?) processes, Grade A is required

Annex 7: Herbal Products

Annex 7, Herbal Medicinal Products, is being revised to incorporate the requirements for APIs in Directive 2004/27/EC and for herbal medicines in Directive 2004/24/EC. The draft of the revised Annex 7 was dated 16 March 2006 and comments were due to be received by the EMEA by 31 July 2006.

The final text of the revised Annex was published on 1 September 2008 and becomes effective on 1 September 2009.

ICH News

ICH Q4B, Annexes

The text of several Annexes to ICH Q4B, Pharmacopoeial Harmonisation, received either Step 2 or 4 approvals at the ICH meeting in June 2008. These Annexes are:

- Annex 2, Extractable Volume of Parenteral Preparations, received Step 4 approval
- Annex 3, Particulate Contamination: Sub-Visible Particles, received Step 4 approval
- Annex 4A, Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests, received Step 2 approval
- Annex 4B, Microbiological Examination of Non-Sterile Products: Tests for Specified Microorganisms, received Step 2 approval
- Annex 4C, Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use, received Step 2 approval
- Annex 5, Disintegration Test, received Step 2 approval

Other News

International Inspection Rationalisation

The FDA and the EMEA have been struggling to resource the required number of overseas inspections. As a result, in November 2007 the EU and USA outlined a pilot project to rationalise international GMP inspections.

The basic idea is as follows:
Each Regulator will identify a contact point specifically for inspection planning purposes. Regulators will outline their preliminary inspection plans for the next 6-12 months. They will provide this information to all other Regulators involved in the pilot. A template for this information could be agreed. Following review of each other's plans, they identify the following:

- If they have previously inspected the site
- If they plan to inspect the site within the same period
- If they have an interest in the site for some other reason (e.g. other products on the market or used in clinical trials in the territory concerned)
- No interest

They will communicate this information in a completed form to the other Regulators involved. Based on the information received and the common areas of interest identified, the regulatory contact points will set up a teleconference to discuss further sites of interest. The object of this teleconference will be as follows:

1. To investigate the possibility that one of the party/parties would undertake to cover the activity of interest to the other party/parties
2. To see whether a joint or coordinated inspection could be organised
3. To see if it is possible for one of the inspectorates to perform the planned inspection and to provide outcomes to the other interested inspectorates

As part of the pilot phase it is proposed to restrict this exercise to inspections of active pharmaceutical ingredients, as most authorities already take a risk-based approach to these inspections and there are less legal complications to taking results of other Regulators into account. Collaboration with the inspectorate of the country where the inspection will take place should also be assured.

The pilot phase should last for 12 months, after which the outcomes should be analysed and a recommendation for future action made.

If the pilot is judged to be successful the following further extensions will be considered:

- Extension to a wider group of Regulators
- Extension to additional types of pharmaceuticals
- Extension to other types of inspection (e.g. GCP, pharmacovigilance)
- Communication of information from regional databases
- Definition of common risk-based criteria and conventions for 'lead' inspectorates

US News

FDA GMP for Phase I IMPs

In January 2006 the FDA published proposals in the US Federal Register, which exempted investigational drugs in Phase I testing from certain GMP regulations. In June 2006 the FDA withdrew the direct final rule after receiving adverse comments from a variety of stakeholders. In July 2008 the FDA issued another final rule on the same subject. The new rule is more detailed than that issued in 2006 and the wording has been revised to improve clarity. It came into effect on 15 September 2008, and applies to small molecule drugs and biologics, including vaccines and gene therapy products, but does not apply to products derived from human cells or tissue.

"*FDA's position is that the GMP regulations were written primarily to address commercial manufacturing and do not consider the differences between early clinical supply manufacture and commercial manufacture.*" For example, the requirements for a fully validated manufacturing process, rotation of stock for drug product containers, repackaging and relabelling of drugs and separate packaging and production areas need not apply to investigational drug products made for use in Phase I trials.

The new exemption does not apply to investigational drugs that are also in Phase II or III examination, or those that are already commercially available but are being assessed at Phase I for alternate indications.
In connection with the final rule on Phase I drug GMPs, the FDA has issued a new document 'Guidance for Industry: cGMP for Phase I Investigational Drugs' recommending approaches to satisfy statutory GMP requirements for such drugs. This document includes standards for facilities and equipment, control of components, testing, stability, packaging, labelling, distribution and record-keeping that are all still absolute requirements.

US Health and Human Services Deputy Secretary Tevi Troy said: "We are tailoring the cGMP requirements to make them appropriate to the earliest stages of drug development." He added that: "This approach will ensure that these investigational products can be developed as efficiently as possible with the highest level of patient protection."

There are many in the European Union, including several people in David Begg Associates, who are sympathetic and supportive of FDA's initiative. However, it further widens the philosophical gulf between the USA and EU regarding the regulatory control of clinical supplies manufacture and creates even more potential for problems when EU inspectors visit US manufacturers of clinical supplies. It should be remembered that, for some biotech companies, the quantities of drug substance prepared for Phase I studies may be sufficient to prepare investigational medicinal products for Phase II studies and even beyond. Under such circumstances, what rules apply?

Given the diverse regulatory opinion on this matter, perhaps it is time for an ICH initiative.

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

The second meeting of the David Begg Associates/University of Strathclyde QP Alumni Association took place in July in York and was a huge success.

The meeting, entitled 'Strategic Issues and CPD for the Quality Professional', was planned and organised by the elected officers of the Association and included invited speakers from Industry as well as former QP trainees. A total of 35 Alumni Association members attended the two day meeting and participated in sessions as diverse as the challenges of technology transfer, outsourcing and contract manufacture to effective change leadership.

Feedback from attendees was superb. Here are just a few of the comments…

"Fantastic 2 days of CPD"

"*Best CPD/network event I've ever been to!*"

"Great speakers"

"Great to include soft skills as well as formal CPD"

"*Excellent event*"

Our congratulations go to the organising committee of the event. The officers of the Alumni Association are creating something truly unique and valuable for this special band of Industry professionals.

If you have completed four or more QP training modules with David Begg Associates and the University of Strathclyde, you qualify for membership of the Alumni Association. If you are not yet a member and would like to benefit from what the Association has to offer, contact Stella Pearson-Smith at **qp@DBA-global.com.**

A reunion spanning seven series of QP training.

Officers of the Alumni with Graham Keen, motivational speaker and 'quiet dresser'!

Kate and Indira, QPs reunited

Congratulations to:

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

Ed Teece, 3M Healthcare Ltd; Neil Smith, Napp Pharmaceuticals Ltd; Barbara O'Dwyer, Pinewood Healthcare Ltd, Ireland; Claire Pierce, GE Healthcare

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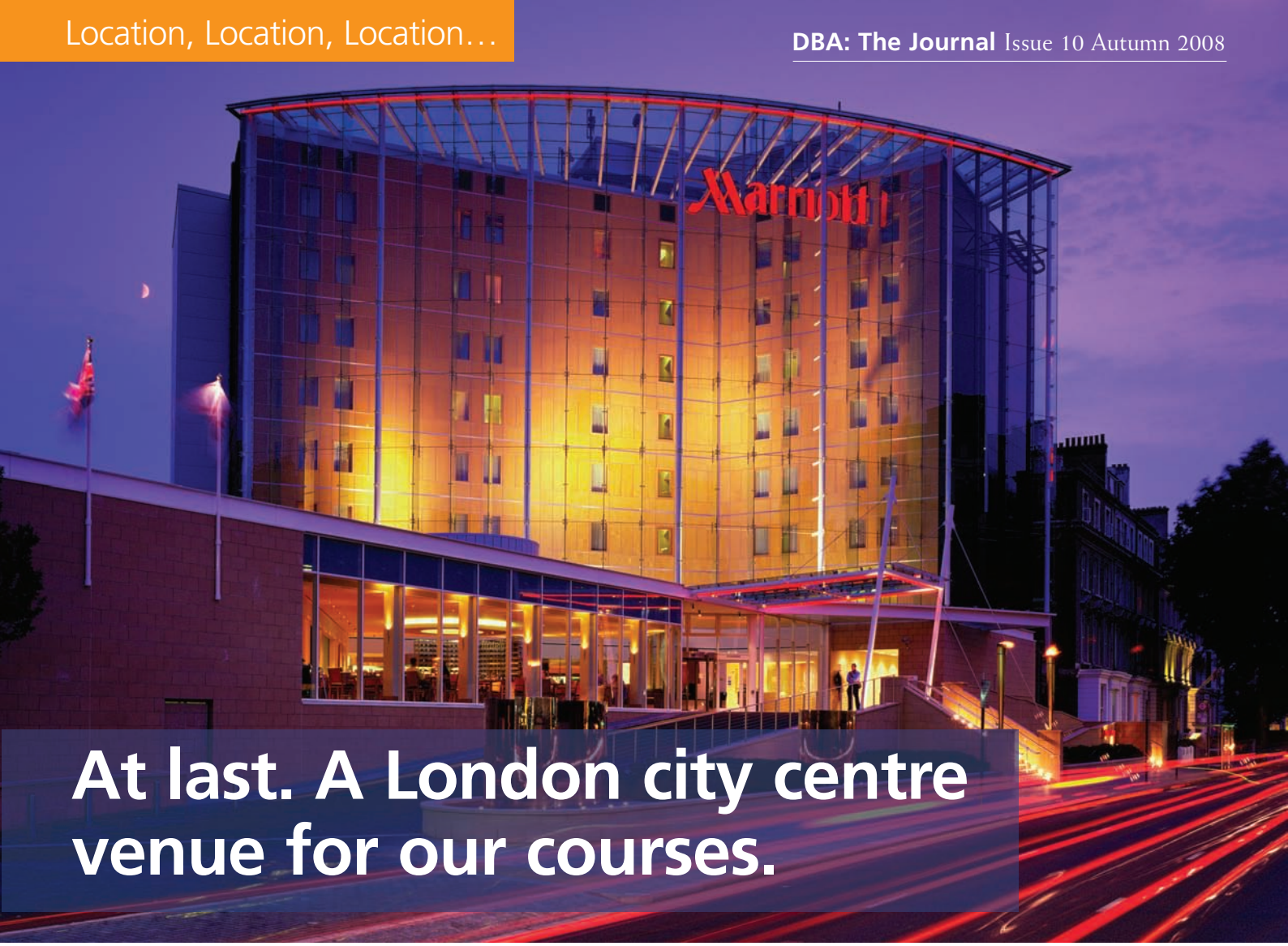

At last. A London city centre venue for our courses.

David Begg Associates is often accused by people in the UK of being "a bunch of Northerners" and it is true that we have traditionally held our training courses in the North of England, in cities such as York and Manchester.

Recently, we have added venues in cities such as Dublin and Amsterdam, and even San Juan and San Francisco, but not London.

It's not true that we have something against London – far from it. But we have struggled to find a London hotel which provides us with the quality of facilities at a price which meets the expectations of our customers – until now!

The Marriott Hotel Kensington offers a very high standard of service and facilities, as you would expect from a member of the Marriott group, but at a price which is similar to our other venues. All bedrooms are well appointed and equipped with high speed internet access to keep you in touch and, when you need to unwind, there is an indoor pool, spa, sauna and gym. The hotel has its own quality restaurant, but nearby there is a wealth of international cuisine available at prices to suit all budgets.

The Marriott is just a short walk from local attractions such as the Natural History Museum and the world famous Harrods department store.

Perhaps more important to our overseas visitors, the hotel is close to Gloucester Road tube station, which provides a direct link to London Heathrow airport and all the main London railway stations.

During 2009 we will be hosting the following courses at the Marriott Hotel Kensington…

Electronic Documentation and Annex 11
3 February

GMP for IT Specialists
4 February

How to Maintain the Validated State of Computerised Systems
5 February

Risk-Based Decision Making for Quality Professionals & QPs
10-11 February

Preparing for the Future: Successful Implementation of ICH Q8, 9 and 10
2-4 June

Good Outsourcing Practice
30 June-1 July

Linking Pharmaceutical Quality and Pharmacovigilance Systems
28 September

Anti-Counterfeiting Measures: Implications for Quality Professionals & QPs
29 September

Practical Aspects of Controlled Temperature Storage and Distribution
30 September-2 October

Senior Management's Role in Driving Quality Improvement for Business Benefit
7 October

Not bad for a bunch of Northerners!

DBA

The Pharmaceutical Training Specialists

Supply Chain Assurance

Time for a Concerted Approach

The now infamous Chinese heparin scandal has had serious repercussions for the global Pharmaceutical Industry and will undoubtedly have even greater consequences in the coming months and years. FDA has reacted by putting permanent staff into China, but regulatory agencies around the world are in agreement that they do not have the skills or resources to monitor the global supply chain. Thus, the major responsibility falls to the dosage form manufacturer to assure the quality of its starting materials. Whilst it is only proper that the user should assure the quality of his or her purchased materials, to place the burden on to individual pharmaceutical companies or, in the case of the EU, the Qualified Person, has some unwelcome consequences:

- Dosage form manufacturers get sucked into a form of 'audit tourism' which is both inefficient and time consuming
- API and excipient manufacturers must devote ever-increasing time and resource to hosting customer audits, to the point where Heads of Quality spend more time managing audits than they do managing quality!

Surely, the time has come to introduce a system of independent, third party certification of API and excipient manufacturers. Such certification could be achieved via independent audits to established and agreed quality standards such as ICH Q7 and IPEC guidance. This, combined with accreditation via EDQM and the various pharmacopoeial standards, could provide dosage form manufacturers with confidence in the quality and GMP standards of suppliers, leaving them free to concentrate their valuable time and resource on issues of specific importance to their products and processes, such as physical properties of materials.

The certification scheme could be centrally funded by Industry organisations and monitored by the regulatory agencies acting in concert, whilst the actual assessment and certification would be performed by approved third party organisations.

Such an approach operates successfully in many other industry sectors, so why not pharmaceuticals? Are we really such a special case?

In the next DBA Journal

Industry News: As ever, we search for regulatory changes so you don't have to; Tech Talk: Microbiological control of non-sterile products – how much is enough? Location, Location, Location…: Things to do in Manchester when you're on a course; DBA People: More things you didn't know about us; Forthcoming Courses: A review of our training courses for Spring and Summer 2009.

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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