DBA

The Journal of David Begg Associates

Issue 11 Winter 2008

New draft FDA guideline on Process Validation

Quality
Leadership
Training

Microbiological control of non-sterile products

– how much is enough?

An NSF International Company

DBA-global.com

welcome

Bob Pietrowski,
Managing Partner
David Begg
Associates

Thanks, Merci, Dank U Wel, Hvala, Muchas Gracias, Takk, Vielen Dank, Xie Xie, Muito Obrigado, Paldies, Tack, Toda, Sukran, Efharisto, Moltes Gràcies, Blagodaria, Kam Sah Hamnida, Kiitos, Achu, Tak, Dziekuje, Spasiba, Gracie, Shukria, Domo Arrigato, Aitäh…

For making 2008 our best year ever!

We know that 2008 has been a very difficult year for the pharmaceutical industry as a whole and many of you have had to work with reduced budgets, so we feel privileged to be able to say that you have made 2008 our best year ever.

It is a source of great pride and professional satisfaction for us to know that when times are tough and money is tight, you turn to us to satisfy your consulting, auditing and training needs.We know that there are many other companies you could use and we want to thank you most sincerely for choosing us.

We also know that 2009 promises to be at least as challenging for the pharmaceutical industry. That is why our services to you in 2009 will actually be cheaper in real terms than they were in 2008. We shared the good times with you, so it's only right that we share the difficult times too.

Despite the doom and gloom that accompanies much of the news we hear these days, everyone at DBA would like to wish you a happy, peaceful and successful New Year.

Bob Pietrowski
Managing Partner

DBA
The Pharmaceutical Training Specialists

Tech talk

Microbiological control of non-sterile products – how much is enough?

Not so long ago, a microbiologist working for a producer of non-sterile medicines had a relatively easy life – a few total viable counts on some incoming materials here, an occasional test on the water system there – all very relaxed and low key.

How life has changed! Now in some manufacturing establishments for non-sterile products, the microbiology department is as highly staffed and as busy as its counterpart in sterile manufacture, carrying extensive tests on incoming materials, intermediates, water systems, production equipment, production staff and extensive environmental monitoring. Ten years ago, seeing a settle plate in a tablet packing area would have been a cause for consternation – now it is relatively commonplace. All this leads me, as a microbiologist, to ask the questions "is all this really necessary?" and "how is it benefiting the patient?"

Our approach to microbiological control of non-sterile products should be essentially the same as to all other policies and strategies in our industry – it should be based upon an objective evaluation of **RISK**. Unfortunately, I believe that, in terms of microbiology, much of what we currently do, and what we are encouraged to do by the regulators, is not based on risk and does not represent good science.

For example, European Council Directive 2003/94/EC on GMP states in Section 5.10

> *"At every stage of processing, products and materials should be protected from microbial and other contamination."*

To what extent should they be protected from microbial contamination? Completely? If so, then all products should be produced sterile; if not, then how much contamination is acceptable. Such "blanket" statements are unhelpful! I think that most of you would agree that, for the vast majority of non-sterile medicines, cross-contamination represents a far greater threat to patient safety than does microbial contamination.

As for FDA, 21CFR211.113 states a requirement for…

> *"Written procedures describing the systems designed to prevent objectionable microorganisms."*

which begs the question "what is an objectionable microorganism?" This is not clearly defined, but it doesn't stop FDA from taking regulatory action; microbial contamination is a frequently cited reason for recalls in FDA-regulated markets, but it is by no means clear whether all these recalled products actually represented a health threat to patients.

Tech talk

In truth, we often over-estimate the risk to patient safety in our industry. Let us be clear; the majority of non-sterile medicines are administered to patients who are, by many criteria, fit and well. If patients were seriously ill, they would not be prescribed tablets, capsules, patches, etc. Thus, people suffering with headaches, muscle or joint pain, raised blood pressure, raised cholesterol, nicotine addiction and similar conditions are not especially at risk of microbiological infection. The microbiological content of their food intake is not monitored, so why should we make such a big deal out of the few grams of medicines they take each day?

Of course, many of you will counter this argument by quoting examples of non-sterile products which are administered to patients with heightened susceptibility to infection, and in these cases I fully agree that some measures need to be taken – this is the essence of RISK MANAGEMENT! However, adopting a "one size fits all" policy is unscientific, inefficient, costly and potentially dangerous in that it may dilute the effort put in to controlling those products and processes which really need it.

As part of a coherent, risk-based approach to the microbiological control of non-sterile products, we need to consider, in addition to the health status of the recipient, the potential sources of contamination as well as risk mitigating factors. Thus, we need to understand the risks from…

- Formulation
- Starting Materials
- Water
- Equipment
- People
- Process Environment

Formulation

All microorganisms require water – and lots of it – to grow. Many non-sterile formulations have very low levels of available water, either because they are dry or solid (tablets, capsules, powders, etc), they are water free (ointments), or they have formulation components which reduce the amount of water available to microorganisms (so-called humectants). It is only those products which contain substantial amounts of water (or intermediates and additives which do) which constitute a significant microbiological threat. Thus, oral liquids, topical liquids, creams, semi-solids, etc constitute a potential microbiological risk, which is why so many of these products are formulated to contain a chemical preservative agent, the efficacy of which is established during development and confirmed periodically on commercial lots.

Thus, the nature of the formulation should be considered as part of the overall microbiological risk assessment.

Starting Materials

As dosage form manufacture consists in the main of mixing and packaging of actives and excipients, it follows that the microbiological content of medicines is derived largely from those starting materials. Thus, it makes sense that microbiological control of starting materials should be the foundation of any control strategy for non-sterile medicines. But, here again, we should apply risk principles and take into account the type of raw materials. Synthetic excipients or actives produced by an aggressive synthetic pathway are unlikely to be contaminated with significant levels of microorganisms as the temperatures, pressures, extremes of pH, etc will have destroyed any contaminants. Only the final stages of preparation, such as crystallisation from water, represent a potential threat. Thus, microbiological monitoring of such materials lot by lot would be excessive and unnecessary. On the other hand, materials of organic or natural origin (starches, sugars, gelatine, gums, etc) are much more likely to carry a high bioburden and pose a much greater risk. Here, increased monitoring and control is warranted, and pharmacopoeial requirements reflect this.

Water

Water is potentially a major source of microbiological contamination, as a poorly designed and controlled water system can contain high numbers of microorganisms, especially Gram negative organisms which may be less susceptible to the killing effect of chemical preservatives. Thus, where water is a key formulation constituent or process component, its control is of crucial importance.

Equipment

If kept clean and dry, process equipment is unlikely to represent a significant source of microbiological contamination to medicines. However, poor design of equipment can result in the presence of "reservoirs" of potential contamination. Thus, the extent of microbiological monitoring of process equipment may range from none to a lot, depending upon the risk factors that exist. Please understand, though, that the best way to control contamination is to remove the potential source (i.e. re-design the equipment).

People

People are often cited as a major potential source of contamination to medicinal products. However, if we exclude sterile products from this discussion, I believe that when certain sensible prevention measures are taken, microbiological risks from people are actually small. An operator would have to bathe in a liquid product to contribute a significant microbiological challenge to it! This is not to trivialise the risk from people, rather it is intended to put it into perspective. Accepted practices of good gowning, good personal hygiene and adoption of clear hygiene practices, allied with instructions to minimise direct contact with product and product contact surfaces, should be sufficient. Actual microbiological monitoring of staff should be regarded, except in exceptional circumstances, as unnecessary and potentially misleading.

Process Environment

If the contribution of people to microbiological contamination of non-sterile products can be considered relatively minor, the contribution from the air is, in the most part, negligible. True, there is a GMP requirement for some liquids and inhaled products to be processed in a controlled environment so as to minimise microbiological contamination, and this is entirely justified on a risk basis, but for the vast majority of non-sterile products, the environment contributes little risk to the product and so microbiological environmental monitoring constitutes at best a luxury and at worst a waste of valuable resource.

Before instituting a microbiological environmental monitoring programme into a non-steriles facility, ask yourself a few questions…

- What am I looking for?
- Where will I monitor, how and how often?
- What is the relationship, if any, between environmental monitoring data and patient risk?
- How much is **unacceptable** and why?
- What is **acceptable** and why?
- What action will I take if results are high?
- How will I assess the effectiveness of that action?

If you cannot answer most or all of these questions, why would you wish to go ahead?

In Summary

1. Effective microbiological control of non-sterile products is essential if we are to assure their fitness for use **BUT** the extent of that control must be based upon an objective assessment of RISK
2. Know your…
   - Products
   - Processes
   - Sources of contamination
   - Mitigating factors
3. Remember that microbiological monitoring is **not** the same as microbiological control
4. Microbiological control strategies should be targeted to providing the following benefits…
   - Better knowledge and control of risk areas
   - Consistently good hygiene practices
   - Elimination of microbiological "hot spots" in processing
   - Reduced risks to patients and not just perceived regulatory compliance
5. Ensure you are adding VALUE, and not just cost

This article represents a very brief, and deliberately provocative, overview of the strengths and limitations of microbiological control strategies for non-sterile products. This topic, and many others, will be discussed in much greater depth in our forthcoming training course "Contamination Control for Non-Sterile Production" to be held in Manchester on 12 – 14 May 2009.

Forthcoming Courses

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

Applying ICH Q10: Pharmaceutical Quality System

Crowne Plaza Hotel, Philadelphia Center City, Philadelphia, 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

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

Book online at www.DBA-global.com

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

DBA The Pharmaceutical Training Specialists

Satisfying EU GMP Requirements for Sterile Products Manufacture

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

This three 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 three 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

Human Error: Causes and Prevention

San Juan Marriott Resort & Stellaris Casino, San Juan, Puerto Rico
24-26 February 2009

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: $2675.00

Practical Application of Quality Risk Management

Amsterdam Marriott Hotel, Amsterdam, The Netherlands
2-5 March 2009

The latest 'hot topic' in GMP! Both the EU and FDA have stated they will use risk assessment in their inspections and expect manufacturers to adopt risk-based quality systems based on guidance provided in ICH Q9, now Annex 20 of the EU GMP Guide. Come and learn what is expected and how to apply risk management techniques to your quality operations.

Course Fee: £2310.00

Formulation & Processing (Part 2)

Qualified Person & Professional Development Training
Hilton York Hotel, York, UK
9-13 March 2009

Continuation 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

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 four months, February 2009 – May 2009

Risk-Based Decision Making

Crowne Plaza Hotel, Philadelphia Center City, Philadelphia, USA
16-18 March 2009

Unfortunately, things don't always go according to plan in our industry, and when they don't we have to make decisions about what to do next. Such decisions must not be based on emotion or 'gut feel', but rather on the basis of facts, scientific understanding and, very important, a clear assessment of RISK. It is fair to say that the regulators judge us not by how we behave when things go right, but by how we act when things go wrong! We will provide you with tried and tested formal risk assessment and risk management techniques to ensure you make the right decisions at the right times! What is more, through a series of scenarios and case studies, we will demonstrate to you how your decision making has improved during the course.

Course Fee: $2675.00

How to Simplify and Improve Your Change Management System

Crowne Plaza Hotel, Philadelphia Center City, Philadelphia, USA
19-20 March 2009

The control of planned and unplanned changes is perhaps the greatest challenge facing any pharmaceutical company and its quality management staff. We will provide you with proven techniques to simplify your change control systems, making them quick and efficient whilst at the same time ensuring compliance with regulatory requirements.

Course Fee: $1775.00

Pharmaceutical GMP

Clontarf Castle Hotel, Dublin, Ireland
23-26 March 2009

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

Course Fee: £2310.00

Practical Aspects of Pharmaceutical Validation

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
2-26 March 2009

This ever-popular four day course will provide you with sound, practical advice on how to organise, document and manage all aspects of qualification and validation to meet international GMP requirements. In addition, validation requirements for specific applications such as cleaning, labelling and packing, computer systems and many more will be covered.

Course Fee: £2210.00 plus VAT

How to Simplify and Improve Your Deviation Management System

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
30-31 March 2009

This focused, two day course will provide you with proven tools and techniques to simplify your deviation management system and improve the quality and effectiveness of your CAPA system, saving you time and money whilst improving regulatory compliance.

Course Fee: £1280.00 plus VAT

EU Requirements for Clinical Trials

San Francisco Marriott Fisherman's Wharf, San Francisco, USA
31 March to 2 April 2009

The European regulatory framework for clinical trials and EU GMP expectations for the manufacture of clinical supplies are the strictest in the world. We will explain the regulations to you and provide you with sound, practical advice on how to comply with EU GMP requirements. If you currently perform clinical trials in Europe, or if you intend to in the future, you should not miss this course.

Course Fee: $2675.00

How to Simplify and Improve Your Change Management System

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
1-3 April 2009

The control of changes is perhaps the greatest challenge facing any pharmaceutical company. We will provide you with proven techniques to simplify your change control systems, making them quick and efficient whilst at the same time ensuring compliance with regulatory requirements.

Course Fee: £1690.00 plus VAT

How to Simplify and Improve Your Batch Record Review Process

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
20-21 April 2009

This focused, two day course will show you how to make your batch record review process effective and value adding – not just time-consuming – and how to organise the batch disposition/product release process for maximum effectiveness and security.

Course Fee: £1280.00 plus VAT

Book online at www.DBA-global.com

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

DBA The Pharmaceutical Training Specialists

Key Performance Indicators for Quality Management Systems

achieve

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
22-23 April 2009

This course will help you to set effective KPIs for your quality management system and will teach you how to review them, interpret them and act upon them to maintain a world class quality system and maximum assurance of product quality and safety.

Course Fee: £1280.00 plus VAT

Pharmaceutical Microbiology

Qualified Person & Professional Development Training
York Marriott Hotel, York, UK
27 April to 1 May 2009

A comprehensive, five day course providing the prospective QP or technical professional with all they need to know about microorganisms, the threat they can pose to product quality and patient safety, how to implement an effective microbiological control strategy and how to assess microbiological risk.

Course Fee: £3105.00 plus VAT

Free Seminar for Prospective QP Trainees

FREE SEMINAR

York Marriott Hotel, York, UK
28 April 2009

Interested in becoming a Qualified Person? 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.

Contamination Control for Non-Sterile Production

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
12-14 May 2009

This course will provide you with practical advice on how to design, maintain, operate, clean and monitor manufacturing facilities, equipment and utilities to minimise the potential for physical, chemical and microbiological contamination of non-sterile dosage forms by application of a risk-based approach. We will help you to add quality, not just add cost!

Course Fee: £1690.00 plus VAT

EU GMP and Inspection Readiness

Renaissance Washington, DC Hotel, Washington, USA
12-14 May 2009

We will explain to you the key differences between US cGMP regulations and EU GMP requirements and provide you with clear advice on how to prepare for an EU inspection, how to manage the inspection to a successful conclusion and how to respond to any inspectional findings.

Course Fee: $2675.00

Human Error: Causes and Prevention

Hilton Manchester Deansgate Hotel, Manchester, UK
12-14 May 2009

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

Course Fee: £1690.00 plus VAT

Engineering Aspects of GMP

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
18-21 May 2009

This highly popular course is designed to provide engineering staff with the knowledge to apply GMP principles to their work and to provide QA staff with an understanding of the special challenges faced by engineering staff.

Course Fee: £2210.00 plus VAT

Satisfying EU GMP Requirements for Sterile Products Manufacture

San Juan Marriott Resort & Stellaris Casino, San Juan, Puerto Rico
19-21 May 2009

Current EU GMP requirements for sterile products manufacture are the most stringent and probably the most confusing on the planet! We will explain the GMP regulations to you, describe the rationale behind them, and advise you on how to comply with them in a pragmatic and cost-effective way.

Course Fee: $2675.00

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

DBA launches modular Quality Leadership training courses in 2009

If pharmaceutical companies are to meet the ever-increasing regulatory and business challenges they face in today's climate, they will need high calibre Quality Professionals throughout the organization and to help the business meet and conquer these challenges and act as change agents through periods of transition.

These Quality Professionals will need the following skills and attributes:

- A comprehensive knowledge and understanding of pharmaceutical legislation – domestic and international – and the compliance issues that face the company and all its staff
- A clear understanding of all the factors which can affect the intrinsic and extrinsic quality of a medicine and how these must be controlled during manufacture
- The ability to use this knowledge to assess risk (to the patient and to the business) and to take risk-based quality decisions
- The leadership skills to communicate decisions effectively, prevent or manage potential conflict and to manage change

Sadly, we are not born with these skills and attributes – they must be taught – and there has been no one organization which can train your key staff in all of these crucial areas: UNTIL NOW!




Quality Leadership Training – Our European Track Record

The skills described above are essentially those required by the Qualified Person in Europe – someone nominated by the pharmaceutical company and formally authorized by the regulatory authorities as being legally responsible for the quality of each and every manufactured lot of medicine or clinical supplies. For the past 19 years, David Begg Associates has provided industry leading training to people wishing to become Qualified Persons and our reputation in this field is second to none. With our partner, the University of Strathclyde in Glasgow, Scotland, we have helped more than 180 industry professionals to become Qualified Persons throughout Europe.

Quality Leadership Training in North America

Over the last six years, we have used this experience in Qualified Person training to work with several US pharmaceutical companies to provide tailored, focused training in-house for specially selected staff. So far, we have successfully completed series of training with two large companies and we have ongoing programs with three more. The feedback from both delegates and senior management has been fantastic…

"We decided that our USA QA colleagues could benefit from the same formalized training as required for QPs in Europe. The results surpassed our expectations. The QA leaders who participated in the training have much greater confidence in their decision-making ability. DBA provided training that could immediately be used in their daily activities."

Gerry Migliaccio, VP/TL Global Quality/EH&S Operations, Pfizer Inc

"DBA's course has made a difference in the short term by allowing our delegates to be more efficient in their daily jobs. Most importantly, DBA has provided them with the skills they will need in the long term to manage change and meet future challenges."

David Watson, Senior Vice President of Global Industrial Operations, Sanofi Pasteur

Quality Leadership Training Through Open Classes

Recently, several US companies have expressed an interest in putting their Quality Professionals through this training, but they have been unable to identify the numbers of students necessary to make in-house training economically viable.

That is why we have decided to offer this training to North American pharmaceutical companies through a series of open residential training courses, commencing October 2009.

We will follow the tried and tested QP training model which has proved so popular and effective in Europe by offering a series of 12 independent but linked training courses over a period of just under two years.

The training courses will be held at the Royal Sonesta Hotel in Boston. Each module will last for three days and will cost $2700.00. DBA's accelerated and interactive learning methods will be used to enhance the learning experience during each of the modules. Instructors will be the same DBA industry experts and University of Strathclyde instructors as in Europe. Additionally, DBA's US experts will ensure that the US regulatory requirements are fully explained.

Delegates attending every module will have the unique opportunity to obtain a Postgraduate Diploma or, if performance is good enough, a Masters Degree in Pharmaceutical Quality and Good Manufacturing Practice from the University of Strathclyde in Scotland.

We will be sending out full information packs on these Quality Leadership training courses in early 2009. If you would like to learn more about this unique training or reserve a place, call Jim Morris on 617-342 3625 or email USinfo@DBA-global.com

Our first US "Human Error" course was an outstanding success

We recently presented our training course "Human Error: Causes and Prevention" for the first time in the USA – it was a huge success!

Delegates went away with a clear understanding of why people make mistakes and, more importantly, with a practical "toolbox" of skills and techniques to reduce costly and potentially dangerous errors in their companies.

Here is just some of the fantastic delegate feedback:

> ***This was the best course I have ever attended. It had great content and was very well presented. For content alone I will be looking for other DBA seminars.***
> Karen Sneed, Astellas

> *What I enjoyed most was seeing how the information provided fits into the larger picture of the quality system. The course provided really useful tools to reduce human error in the Pharma industry.*
> Cheryl Kirkman, Pfizer

> **An outstanding course with excellent delivery! Very nice mix of lectures and group discussions providing facilitated learning from the tutors as well as industry peers.**
> Bill Blunt, Amgen

> ***The course material and the course tutors were fantastic. Probably the best seminar I have ever attended. Practical and straightforward… the 'real deal'!***
> Tony Stuckwisch, UCB

> ***The tutors were really great and answered all our questions. The course really re-emphasises the importance of ICH Q9 and Q10.***
> Tiffany Coleman, Aptuit

> *Excellent course with some great practical examples. Highly engaging.*
> Matt Peplowski, Bristol-Myers Squibb

> I thoroughly enjoyed the course! I have some great action points to work on.
> Linda Clark, UCB

If you missed this unique course this time round, don't worry. We will be hosting it again in Puerto Rico from 24 to 26 February and in San Francisco from 3 to 5 November.

If you want to come to the UK, we are hosting the course in Manchester from 12 to 14 May.

We hope to see you soon.

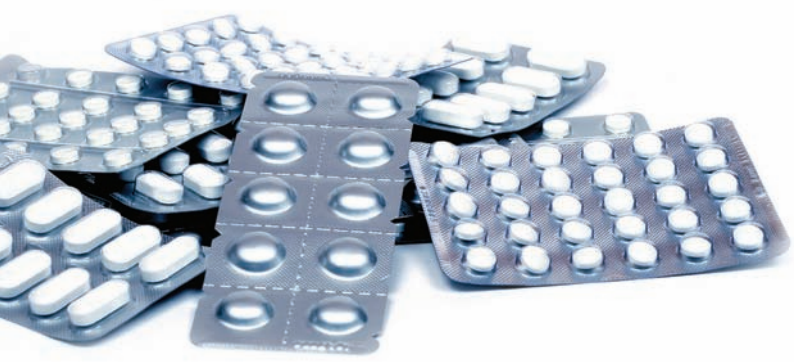
Industry News

'Atypical' APIs

The Commission and the EMEA have recognised that for a small number of medicinal products the primary use of the active substance is not in a medicinal product and the producer may therefore not be aiming to meet the specific requirements of pharmaceutical customers that represent an insignificant volume of business. This issue has been the subject of discussions between the Commission/EMEA and various industry groups for some time. In September 2008 the EMEA issued the following advice on the Q&A section of their website on how to proceed when dealing with an 'atypical' active:

"Alternative sources should normally be sought but in exceptional circumstances the manufacturing authorisation holder should assess and document to which extent GMP is complied with and provide a risk-based justification for the acceptance of any derogation. The declaration provided by the Qualified Person should set out in detail the basis for declaring that the standards applied provide the same level of assurance as GMP. EMEA will collect experience with this approach which can be used as a basis for discussion on related amendments to guidelines in the future."

This is a pragmatic solution that has generally been welcomed by industry.



EU News

FDA Seizes Contaminated Heparin from US Manufacturer

FDA recently instructed US Marshalls to seize five lots of Heparin Sodium API and six lots of Heparin Lithium (for use in medical devices) from Celsus Laboratories Inc in order to "prevent this contaminated heparin finding its way into the market place". The heparin was of Chinese origin and had been found to be contaminated with the now infamous over-sulphated chondroitin sulphate (OSCS).

This tough action by FDA highlights the importance of supply chain Quality Assurance – something all manufacturers on all continents must place at the top of their strategic agenda.

European Parliament Vote Paves Way for Radical Revision of Variations Procedure

On 22 October, the European Parliament voted heavily in favour of a Commission proposal which would prepare the ground for a radical overhaul of legislation governing variations to marketing authorisations in the EU to make the system clearer, simpler, harmonised and more flexible.

EU Survey of Procedures to Assure APIs are Manufactured to GMP

The EMEA has published the results of a survey conducted in 2005 and 2006 to determine the extent to which dosage form manufacturers are complying with their obligation to assure that active substances are being prepared in accordance with GMP.

The report concludes that the majority of manufacturers have adopted procedures, such as audit programmes, to ensure compliance, but there is a concern regarding measures taken by importers and small companies. The agency recommends more attention by the member state authorities in these cases.

The report also contains an aide-mémoire for auditing active substance manufacturers.

MHRA Publishes Good Pharmacovigilance Practice Guide

The UK's regulatory authority (MHRA) has recently published a guideline on Good Pharmacovigilance Practice, which should be of interest to anyone involved in implementing or auditing systems for pharmacovigilance and ADR reporting.

Industry News

New draft FDA guideline on Process Validation – a real step forward

FDA published its new draft guidance on process validation in November 2008. When adopted, it will represent a major step forward in approach to process validation and bring the industry into the 21st Century. As such, it represents one of the most important guidance documents to come from a regulatory agency in many years.

The existing FDA guidance was published in 1987, so it is no surprise that the new guidance is very different from what is currently in place – what is really pleasing is that the draft document embraces the new thinking, exemplified by ICH Q8, 9 and 10 and makes a clean break from the outmoded and unscientific philosophy of the previous guidance. Gone are the outdated concepts of "worst case validation" and "re-validation". Instead, we have forward-looking principles such as "Process Control Strategy" and "Continued Process Verification".

A New Definition of Process Validation

The 1987 guidance document defines validation as…

> *"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes."*

The new draft guidance contains a subtly different definition of process validation…

> *"The collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products."*

This definition encompasses the life-cycle approach to pharmaceutical quality management. In essence, it says that process validation is a journey, not an event!

This subtle but important change in philosophy underpins the whole of the document – and represents perhaps the greatest conceptual challenge to traditional pharmaceutical thinking.

The Stages of Process Validation

The 1987 guidance recognises four distinct stages in process validation…

1. Equipment: Installation Qualification
2. Process: Performance Qualification
3. Product: Performance Qualification
4. Timely Revalidation

Inherent in this categorisation is the recognition of the importance of process and equipment design and the importance of a multi-disciplinary approach, but the document specifically excludes development scientists. By contrast, the new draft states…

> *"A successful validation programme depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control that is appropriate for the manufacturing process.*
>
> *Manufacturers should…*
>
> - *Understand the sources of variation*
> - *Detect the presence and degree of variation*
> - *Understand the impact of variation on the process and ultimately on product attributes*
> - *Control the variation in a manner commensurate with the risk it represents to the process and product"*

It goes on to say…

> *"Focusing on qualification efforts without understanding the manufacturing process may not lead to adequate assurance of quality."*

Consequently, the draft guidance recognises the following key stages in process validation…

1. Process Design
Definition of the process based on knowledge gained through development and scale-up activities

2. Process Qualification
Confirmation that the process design is capable of reproducible commercial manufacture

3. Continued Process Verification
Ongoing assurance, gained during routine production, that the process remains in a state of control

Process Design

Process design is not an explicit component of the 1987 guidance. It involves two important phases…

- Building and capturing process knowledge and understanding
- Using that knowledge and understanding to establish a strategy for process control, which may or may not incorporate PAT principles

The process design stage delivers "the operational limits…to be carried forward to the next stage for confirmation"

Process Qualification

This has two elements…

- Design of the facility and qualification of the equipment and utilities – what is currently usually referred to as installation qualification (IQ) and operational qualification (OQ)
- Performance qualification (PQ)

The new document states…

> *"The approach to PQ should be based on sound science and the manufacturer's overall level of product and process understanding."*

It goes on to say…

> *"It is not typically necessary to explore the entire operating range at commercial scale if assurance (of product quality) can be provided by other data."*

In other words, process validation is distinct from process definition and, if the process is sufficiently understood and defined, then perhaps there is no need for so-called "worst case" validation.

Three is NOT a Magic Number

Although never mentioned in FDA guidance, the principle of three consecutive acceptable batches has been implicit in FDA's (and industry's) traditional expectations for process validation. The draft document effectively consigns that approach to the dustbin of history. Instead, it requires that the manufacturer defines "criteria that provide for a rational conclusion of whether the process consistently produces quality products. The criteria should include…

- A description of the statistical methods to be used in analysing all collected data (e.g. statistical metrics defining both intra-batch and inter-batch variability)
- Provision for addressing deviations from expected conditions and handling of non-conforming data. Data should not be excluded from further consideration in terms of PQ without a documented, science-based justification".

The final nail is driven into the coffin of the three consecutive batches dogma by the rather controversial statement…

> *"We recommend continued monitoring and/or sampling at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates. Once the variability is known, sampling and/or monitoring should be adjusted to a statistically appropriate and representative level."*

Many may view this recommendation as a request for even more sampling and testing than is currently performed during validation studies, and hence even more expense. However, if it is done well, validation under the new guidance clearly provides for the adoption of ongoing sampling and testing strategies which are less intensive and hence less expensive. Thus, there is the potential for long term gain in exchange for what some may consider short term (scientifically justified) pain.

Continued Process Verification

Having confirmed that the process design is capable of reproducible commercial manufacture, the manufacturer must **continually** assure that the process remains in a state of control throughout commercial manufacture. Thus "an ongoing programme to collect and analyse product and process data that relate to product quality must be established". The draft guidance goes on to say that "the data should be assessed periodically to determine whether requalification should be performed and the extent of that requalification".

Whilst this guidance is fundamentally similar to that in the 1987 document, the new draft makes particular reference to the use of statistics in assessing continued control and prefers the word "requalification" to "revalidation".

How Does the New Draft Compare with EU Guidance?

EU guidance on process validation is to be found primarily in Annex 15 of EudraLex Volume 4, the so-called EU guide to GMP. By comparison, it must be said that Annex 15, which was adopted in 2001, is tired and out of date. It does not embrace recent ICH initiatives, which is not surprising as it pre-dates them, and so makes no mention of the importance of development activities in product and process development. Nor does it reference PAT principles.

Annex 15 references "retrospective validation", which FDA clearly regards as no longer acceptable and, perhaps most importantly, differs from the FDA guidance in perpetuating the "three batches" dogma.

> *"It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters would constitute a validation of the process."*

Other areas of significant variance to the new FDA draft include…

- The requirement for process validation batches to be the same size as the intended industrial scale batches
- The requirement to revalidate sterilisation processes at least annually.

Perhaps it is time to review Annex 15 and related guidance.

In Summary

The new FDA draft guidance represents, in our view, a real step forward in establishing that process validation is a continuous process that begins in Development and ends when the product and/or process is finally retired. It is truly a journey and not an event!

Whilst some may struggle to accommodate the consequences of this new approach, its adoption will ultimately benefit both the industry and the patient.

By comparison, current EU guidance now seems woefully out of date.

The draft FDA guidance, along with current and future expectations for process validation and how to meet them, will be covered in depth in our training course, "Practical Aspects of Pharmaceutical Validation" to be held in Manchester, UK on 23 - 26 March 2009.

DBA

The Pharmaceutical Training Specialists

QP Issues

DBA's first meeting for sponsors is a huge success

As part of our ongoing commitment to the training and development of Qualified Persons in the European Union, we regularly hold free seminars for people who wish to learn more about becoming a QP.

In the UK at least, everyone applying for QP status requires their application to be "sponsored" by an existing QP, who vouches for the applicant's knowledge, education and, in particular, their character and suitability for the role. QP assessors rely to a great extent on the information provided by the sponsors when considering candidates' overall eligibility and suitability for QP status. Sadly, it must be conceded that the quality of the information provided by sponsors is presently very variable.

That is why we at DBA decided to hold a free seminar for people acting, or expecting to act, as a sponsor for a trainee QP. The objective behind the meeting was to ensure that those who attended gained a clear understanding of the professional responsibilities of the sponsor; to the trainee QP, to the three professional bodies which administer QP eligibility in the UK, and to the UK's regulatory agency, MHRA.

A total of 14 current and potential sponsors heard presentations from John Johnson, representing the QP Assessors and professional bodies, Sam Clack, representing the QP student group of the UK Pharmaceutical Quality Group, and Bob Clark, QA Director of Napp Pharmaceuticals and an experienced sponsor.

The presentations provoked prolonged and vigorous discussion. Everyone who attended agreed that it had been a very valuable day, which DBA should turn into an annual event.

And the overall conclusion – it was generally agreed that, while the QP students are working hard and performing well, their sponsors – in many cases – could do better. Everyone felt that there should be more training and support for sponsors and DBA was urged to help – something we are more than happy to do. Watch this space!

If you would like to learn more about how DBA can support you in your sponsor role, call Mike Halliday on +44 (0) 1751 432999 or email him at qp@DBA-global.com

We apologise…

In the last issue of the DBA Journal we printed a photograph of Kate Krachai and Karam Dhaliwal enjoying the evening. Unfortunately, the caption to the photograph read "Kate and Indira, QPs reunited"

Karam, please accept our most sincere apologies. We were devastated when we spotted the error.

In the next DBA Journal

Industry News: As ever, we search for regulatory changes so you don't have to; Tech Talk: Supplier Quality Assurance; Location, Location, Location…: Things to do in Manchester when you're on a course; DBA People: New arrivals; Forthcoming Courses: A review of courses for Summer and early Autumn 2009.

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

David Begg Associates

Europe The Georgian House, 22-24 West End, Kirkbymoorside, York, UK, YO62 6AF
Tel: +44 (0)1751 432999 Fax: +44 (0)1751 432450 Email: mail@DBA-global.com

USA Suite 19, 101 Federal St., Boston, MA 02110, USA
Tel: 617-342 3625 Fax: 617-342 3623 Email: USinfo@DBA-global.com

DBA-global.com