DBA

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Human Error: Causes and Prevention

Martin Lush explores why people make mistakes and what can be done to reduce errors in the workplace

David Begg associates
The Pharmaceutical Training Experts

Happy New Year 2008

**Bob Pietrowski,
Managing Partner
David Begg
Associates**

We hope you had a wonderful Christmas and New Year break. Such a shame to be back at work!

This is traditionally a time when people make resolutions for the coming year. As well as the usual ones – lose weight, exercise more, drink less – which are often abandoned before February, perhaps you will consider professional resolutions for you or the people who work with you – "increase my knowledge and professional contribution and that of my team", for example.

If you do, then our extensive range of training courses may be of interest to you. For a full 2008 listing, please visit our website. We are constantly adding new topics and new venues to our listing as we take DBA worldwide, so please watch the web for new additions. To help you keep up to date, we will be re-issuing an updated version of our 2008 Training Course Programme in the coming weeks.

As for my New Year resolution, you won't be surprised to learn that it involves education! I intend to give more of my time and my money to helping others gain a basic education, by sponsoring schools and schoolchildren in Africa.

Have a wonderful year!

Bob Pietrowski
Managing Partner

David Begg associates
The Pharmaceutical Training Experts

Tech talk

Martin Lush explores why people make mistakes and what can be done to reduce errors in the workplace

Human Error: Causes and Prevention

Every year, the pharmaceutical industry wastes huge sums of money as a result of mistakes in the workplace – so-called "human error."

Human error is often cited as the cause of product recalls, customer complaints, batch rejects, deviations and adverse audit findings. In most cases, however, human error is not the root cause, just a convenient excuse.

The good news is that such costly and risky mistakes can be prevented if you follow some very simple and practical rules.

- **Rule One:**
  Understand the "Psychology" of Human Error

  Why is it women are better at certain tasks than men? Why do we see only what we want to see? Why do we all make assumptions that result in mistakes being made? How can you prevent mistakes due to boredom? What "situations" and tasks actually encourage the brain to make the wrong decision?

  The answers lie in understanding the psychology of human error.

- **Rule Two:**
  Adopt a Positive, Blame-Free Attitude to Mistakes and Errors

  Every mistake is a free and invaluable lesson on what not to do! Providing, that is, you learn from the experience and don't do it again!

  By creating a blame-free environment so that errors can be reported and prevented, you can go a long way towards stopping those deviations that just keep coming back again and again.

- **Rule Three:**
  Drive Out Complexity in Everything at Every Level

  As complexity increases so does the number of mistakes. The pharmaceutical industry excels at overcomplicating the simplest of tasks and procedures. This costly and unnecessary complexity actually encourages people to make mistakes.

  The answer? Keep things as simple as possible! Make the time to review and simplify your processes, procedures and systems (bearing in mind the psychology of human error) and you will see real benefits.

Tech Talk

- **Rule Four:**
  Focus on User-Centred Design

Equipment procedures, processes and systems that work have one thing in common. They are designed by the users. This is far from easy.

By involving the users from the outset and adopting the principles of "user-centred design" it is possible to reduce the size of a batch manufacturing record by up to 50% and massively reduce documentation errors. Similarly, you can make SOPs easier to follow.

- **Rule Five:**
  Build in Plenty of "System Safeguards"

When something goes wrong you must have plenty of system safeguards in place. These are designed to either prevent the error at source or to stop it getting through undetected.

You rely on your Quality System to do this. You all have systems for training, validation, maintenance, QC analysis, deviation reporting, audits and self-inspections, to name but a few. But do these system safeguards always work? Not according to the FDA and EU regulatory agencies that cite deficiencies in Quality Systems in their "top three" regulatory concerns.

It is not how many system safeguards you have in place that is important, but choosing the right ones! Take the time to ensure that your safeguards are relevant, focused on the quality critical factors and above all are effective.

- **Rule Six:**
  Remove "Risk Increasing Factors"

Factors present in our working environment can cause human error. These "stressors" can range from poor lighting, complex documentation, inconsistent processes, illogical material flows through to company culture, inadequate communication and inaccurate and insensitive performance measures.

Risk Increasing Factors (RIFs) must be identified and removed by using techniques such as RIF Audits, Failure Mode & Effect Analysis and Process Flow Evaluation.

- **Rule Seven:**
  Make People Responsible and Accountable

With responsibility and accountability come pride, ownership and discipline. The result? Very low error rates. As companies become larger and more "impersonal", individual responsibility and accountability can be easily lost, with disastrous consequences. Don't ever let this happen!

- **Rule Eight:**
  Focus on "Educating" your Workforce

"Your products are only as good as the people making them. Education is thus central to reducing error. It is essential to understand the difference between education and training. A dog can be trained to sit up and beg, but it doesn't understand what it is doing or why it is doing it. You want educated staff, not trained staff!

Your training materials and training sessions should…

- Take due account of the importance of the brain's "reticular activating system" in effective learning
- Satisfy all four adult learning styles
  1. Auditory/visual
  2. Visual/intellectual
  3. Intellectual/somatic
  4. Somatic/auditory
- Ensure "whole brain" training – that stimulates both the left and right sides of the brain

If they don't, you are not getting the most out of your training programme.

Do you want to learn more about how to apply these eight rules in an integrated way to reduce human error, increase "right first time" quality, reduce reworks, rejects and recalls and improve compliance?

If you do, you should attend our new two day training course "Human Error: Causes and Prevention" to be held in Manchester on 13 and 14 May 2008.

New DBA People

We are delighted to announce that Stewart Green joined us as an Associate Consultant on 1 January 2008.

Prior to joining us, Stewart was Director of Quality for Wyeth UK, based at the company's manufacturing site in Havant on the south coast of England.

A microbiologist with a degree in Applied Biology and a Masters in Strategic Quality Management, Stewart has over 40 years' experience in the pharmaceutical industry, encompassing research, validation, logistics/supply chain management, quality control and quality assurance. The last 20 years of Stewart's career have been spent in Quality Assurance, covering medical devices, oral solids and liquids, vaccines and biotechnology products.
He has extensive hands-on experience of most forms of sterile processing.

Stewart is currently Chair of PharMIG (Pharmaceutical Microbiology Interest Group) in the UK and also sits on the British Pharmacopoeia Antibiotics Experts Group and the British Standards Institute (BSI) Clean Room Standards Group. He was also a committee member of the UK's Pharmaceutical Quality Group for many years.

Stewart has been an active Qualified Person since 1980 and, as a named QP, has participated in numerous MHRA and EMEA inspections in the UK and USA.
He has also acted as the Quality Expert on the CMC section of more than 50 regulatory submissions.

As you can see, Stewart has a wealth of practical experience to offer and we are delighted to welcome him to the DBA team. We are sure that his arrival will help us to improve further the quality and breadth of services we offer.

DBA in Singapore

We have targeted 2008 as a year of international growth for DBA.

Our first training courses in Puerto Rico and USA have created an excellent level of interest and now, flushed with success, we have decided to take our first steps into Asia and the Pacific Rim by running courses in Singapore.

In addition to having a thriving pharmaceutical industry of its own, Singapore is centrally located for pharmaceutical companies in Australasia and much of the developing Pacific Rim region. Over the last year we have seen a significant increase in delegates from this region attending our courses in Europe, so it seems logical to take our courses to them rather than expect them to fly to us!

Our first training course in Singapore will be…

- Pharmaceutical GMP
  20 – 23 October 2008

We have yet to finalise a location for this course, but we intend to follow our usual practice of selecting a high quality, city centre hotel.

Further details will be published in our next issue of the Journal and in the News section of our website.

Forthcoming Courses

What's planned for the next five months, March – July 2008

Pharmaceutical Risk Management
Amsterdam Marriott Hotel, Amsterdam, The Netherlands
3 – 6 March 2008
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, "Pharmaceutical Risk Management". Come and learn what exactly is expected and how to apply risk management techniques to your quality operations.
Course Fee: £2541.00

Quality Management Systems
Qualified Person & Professional Development Training
Hilton York Hotel, York, UK
10 – 14 March 2008
Designed to provide the prospective Qualified Person or any pharmaceutical professional with all they need to know to be able to design, implement, monitor and maintain a cost-effective quality management system to current international regulatory requirements, including the imminent ICH Q10, "Pharmaceutical Quality Management Systems".
Course Fee: £2960.00 plus VAT

The Role & Duties of the Qualified Person
The Imperial Riding School Vienna
A Renaissance Hotel, Vienna, Austria
11 & 12 March 2008
This course provides essential guidance, not just on the legal duties of the Qualified Person, but also on how the QP should organise themselves, their colleagues and the quality system to ensure that they fulfil their duties with skill and professionalism in the best interests of the patient and their employer.
Course Fee: £1280.00 plus VAT

Qualified Person & Professional Development Training
FREE SEMINAR
Hilton York Hotel, York, UK
11 March 2008
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.

Practical Aspects of Pharmaceutical Validation
Manchester Marriott Victoria & Albert Hotel, Manchester, UK
31 March – 3 April 2008
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

Deviation Reporting and CAPA
Clontarf Castle Hotel, Dublin, Ireland
31 March & 1 April 2008
This two day course is designed to provide you with the tools and skills to identify, correct and report the root cause of quality management problems quickly and efficiently so that you can demonstrate that your CAPA systems work!
Course Fee: £1505.00

EU GMP Requirements for the Manufacture of Sterile Products
PUERTO RICO
San Juan Marriott Resort & Stellaris Casino, San Juan, Puerto Rico
1 – 3 April 2008
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: $2625.00

Batch Manufacturing Records and Product Release Procedures
Clontarf Castle Hotel, Dublin, Ireland
2 & 3 April 2008
This focused, two day course will show you how to make your batch review processes 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: £1505.00

Book online at www.david-begg-associates.com

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The Pharmaceutical Training Experts

Key Performance Indicators for Quality Management Systems

NEW COURSE

Manchester Airport Marriott Hotel, Manchester, UK
15 & 16 April 2008

This brand new course will help you to set effective KPIs for your quality management system and 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

European Pharmaceutical Legislation and the Role of the Qualified Person

USA

San Diego Marriott Hotel & Marina, San Diego, California
15 – 17 April 2008

This three day course will explain the EU regulatory framework for pharmaceuticals, the major differences between EU and US GMPs and regulatory inspections and, most importantly, we will explain the crucial role of the EU Qualified Person and how the N. American pharmaceutical manufacturer must interact with the QP to facilitate the sale and supply of products to the EU.

Course Fee: $2625.00

Pharmaceutical GMP

Clontarf Castle Hotel, Dublin, Ireland
21 – 24 April 2008

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

Course Fee: £2540.00

Contamination Control for Non-Sterile Production

NEW COURSE

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
29 April – 1 May 2008

This brand new course will provide 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 practical application of a risk-based approach. We will help you to add quality, not just add cost!

Course Fee: £1690.00 plus VAT

Formulation, Manufacturing, Analysis

Qualified Person & Professional Development Training
University of Strathclyde, Glasgow, UK
12 – 16 May 2008

Only by making and testing medicines can you learn what processing steps and parameters are really critical to quality. This practical course will enable you to learn for yourself how subtle changes in starting materials, formulations and processing conditions impact upon the performance of a range of sterile and non-sterile dosage forms. Essential experience which is becoming harder to gain in industry alone!

Course Fee: £3115.00 plus VAT

Human Error: Causes and Prevention

NEW COURSE

Manchester Airport Marriott Hotel, Manchester, UK
13 & 14 May 2008

Human error is a commonly quoted cause of problems and deviations in our industry, but often it is not the real reason, but a convenient excuse, and corrective actions such as "retraining" are doomed to failure. You know this, and so do the regulators! This new and 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: £1280.00 plus VAT

Engineering Aspects of GMP

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
19 – 22 May 2008

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

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

Call us on: +44 (0) 1751 432999 or email: courses@david-begg-associates.com

Forthcoming Courses

What's planned for the next five months, March – July 2008

EU GMP Requirements for the Manufacture of Sterile Products

USA

San Diego Marriott Hotel & Marina, San Diego, California
27 – 29 May 2008

This three day course will teach you the important differences between EU GMP expectations for sterile products and those of the FDA, including why EU inspectors put such great emphasis on the zoning principle for facilities, steam sterilisation and air removal and environmental protection for activities such as sampling, filtration and capping. Essential for any company supplying sterile products to Europe!

Course Fee: $2625.00

Effective Pharmaceutical Audits and Self-Inspections

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
9 – 12 June 2008

Learn how to carry out audits with skill and sensitivity, whilst ensuring that you do not overlook important issues. This course will help you to make your audits really value adding. Plus, have the opportunity to become a DBA certified auditor.

Course Fee: £2210.00 plus VAT

Investigational Medicinal Products

Qualified Person & Professional Development Training

Hilton York Hotel, York, UK
16 & 17 June 2008

Designed to provide the prospective Qualified Person or pharmaceutical professional with an up to the minute understanding of EU regulations for the conduct of clinical trials, the GMP expectations for the manufacture and control of clinical supplies and the key role of the QP.

Course Fee: £1250.00 plus VAT

The Role & Professional Duties of the Qualified Person

Qualified Person & Professional Development Training

Hilton York Hotel, York, UK
18 – 20 June 2008

This course provides essential guidance, not just on the legal duties of the Qualified Person, but also on how the QP should organise themselves, their colleagues and the quality system to ensure that they fulfil their duties with skill and professionalism. Includes a review of the UK QP assessment process and a simulated QP assessment interview.

Course Fee: £1810.00 plus VAT

Key Topics in Sterile Products Manufacture:

A Practical Interpretation of Annex 1

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
23 June 2008

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

Course Fee: £675.00 plus VAT

Environmental Monitoring for Sterile Products Manufacture

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
24 & 25 June 2008

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

Course Fee: £1280.00 plus VAT

Process Simulations

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
26 June 2008

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

Course Fee: £675.00 plus VAT

Outsourcing

NEW COURSE

Manchester Marriott Victoria & Albert Hotel, Manchester, UK
30 June – 3 July 2008

Practical advice to ensure that outsourcing of manufacture, testing, qualification, validation, and any other activity is a success and not a disaster! We will tell you the current GMP requirements and provide you with best practices for selection, contractual issues, documentation, control and review of all outsourced activities.

Course Fee: £2210.00 plus VAT

Pharmaceutical GMP

ADDITIONAL LOCATION

The Imperial Riding School Vienna A Renaissance Hotel, Vienna, Austria
14 – 17 July 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". Located to provide local training for companies in Central and Eastern Europe.

Course Fee: £2235.00 plus VAT

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

Call us on +44 (0) 1751 432999 or email: courses@david-begg-associates.com

Book online at www.david-begg-associates.com

Qualified Person and Professional Development Training – Series Ten

Series Ten: Same High Quality Training – Some New Incentives

October sees the commencement of our tenth series of training modules for the aspiring QP.

Over the past 18 years, we have helped 176 people to become QPs – a statistic which gives us immense pride.

We know that we are in the fortunate position of being considered the premier provider of QP training. We also know that we are by no means the cheapest – although we like to think that you get what you pay for. Nonetheless, we appreciate that the pharmaceutical industry is going through a period of belt tightening and, whilst QP training represents a critical undertaking which will only be done once and so should be done right, we understand that budgets are not limitless.

That is why we have decided to help you by introducing some new initiatives for Series Ten…

- A clear pricing structure for all modules, published in advance so that you know exactly what the training will cost over the next two years.
- If you send more than one delegate from the same site to any of our modules, then the second and subsequent attendees will receive a 20% discount on the course fee.
- Delegates from national health services and all representatives from government regulatory agencies shall receive a 50% discount on the course fee.

We hope that these offerings will assist you in budgeting for your QP training needs.

Full details of Series Ten will be published shortly.

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

The first meeting of the QP Alumni Association was held in York last summer, and the turnout was tremendous!

Membership of the Alumni Association is free and is open to anyone who has attended four or more of our QP training modules – the first meeting attracted 55 attendees from five different countries.

The meeting provided a wonderful opportunity for old friends to get together again, often for the first time since they completed their QP training, but it wasn't just a social gathering – over the two days the attendees discussed topics of burning interest to the practising QP, including whether we expect too much of today's QP.

In addition to talks from the usual suspects at DBA, there were presentations from members of the Alumni Association:

- Annie Rietveld, currently Head of the GMP Inspectorate for The Netherlands, gave a personal view of the current role of the QP in Europe.
- Paul O'Connor, now Global Vice President of Quality for Almac Clinical Services, spoke on the special challenges facing the QP for investigational medicinal products.
- Boudy König, Director of Third Party Quality Assurance with Centocor, gave a graphic description of what it is like to be a QP in a global supply chain.

The meeting began with a keynote speech from David Watson, Senior Vice President of Global Industry Operations for sanofi pasteur, who gave some very useful advice to QPs on their role in adding value to organisational performance. All of the audience could be seen examining their personal characteristics to determine whether they fitted the description given by David of the "precious" QP, who can be so damaging to the organisation!

A synopsis of David's talk is reproduced on the following pages.

At the end of the meeting, the attendees agreed that it had been a valuable two days and unanimously voted to repeat the event in July 2008 (watch this space!).

It was also agreed that the next meeting would be organised by elected officials of the Alumni Association. Those elections have since taken place and we are delighted to announce the results…

Chair:	**Tony Mayhall**
Deputy Chair:	**Neil Banks**
Overseas Officer:	**Mirjam te Koppele**

Members of the Association are encouraged to contact the officials (through us if necessary) to suggest topics for the next meeting.

All in all, a great start to what we hope will be an important and influential Association!

The following is a synopsis of David Watson's keynote talk to the QP Alumni Association

The Role of the Qualified Person in adding Value to Organizational Performance

1. Background

The release to market of each batch of product, in compliance with the marketing authorization, must be approved by a "Qualified Person"; it is a mandatory requirement in order to be able to supply products within the pharmaceutical and healthcare sectors. That person must have the academic qualifications, experience and position within the organization to exercise his/her responsibilities effectively. Therefore, much time, effort and expense is directed towards training those wishing to take on these duties.

Quality professionals have both a policing role and an influencing role; the first being to ensure that risks to the business are minimized, so that compliance is maintained and the marketing and manufacturing authorizations are protected; the second, by virtue of their position in the business, to see where and how the products and processes can be made more secure and efficient, so reducing costs, shortening lead times and enhancing customer satisfaction.

To do this, the organizational positioning of the QP within the business is critical – but organizational authority has also to be matched by "authority by influence." The QP educational program provides the technical answers. To maximize added value within the organization, these need to be wedded to much wider management skills and capabilities.

2. The Industry is Highly Regulated

To operate in the pharma and healthcare industries, strict standards have to be applied and followed. These are becoming more exacting day by day, as companies have to meet the expectations of more and more regulatory agencies, a variety of pharmacopoeias and other standards institutions, and face up to the challenges of new technical and regulatory initiatives. The QP has to operate against this changing background.

3. The Duties of the QP

The development of the regulations and the concept of the role of the QP in the pharma industry emerged in the mid 70s to early 80s.

In terms of the legal duties and responsibilities of the QP, not a lot has changed since those early days. However, a huge change has taken place in the authorities and their attitude to risk and flexibility of decision making. There exists today almost no flexibility of interpretation of data against the experience and knowledge of those making the decisions within the commercial organizations. Any deviation from the registered specification, no matter how low in risk, usually requires a license variation. There have been several recent examples where QPs have been sanctioned by MHRA and their professional bodies in this respect. So it's a fact of life that the role of the QP is tougher now than it was 25 years ago!

4. Where Can QPs Add Value?

Firstly, the primary role of the QP is to "**protect value**." Ensuring compliance with regulatory authority requirements protects not only the "license to operate" and the company reputation, but also the market value of the company. Serious regulatory issues can wipe considerable value off the total market capitalization of the company. This should never be forgotten as we carry out our duties.

Secondly, the QP has a unique opportunity to see the "**outcomes**" of the business. The "added value" process is complete when the finished product is ready for release to the market, generating sales and profit. Batch documentation provides the whole history of how this value added process was achieved.

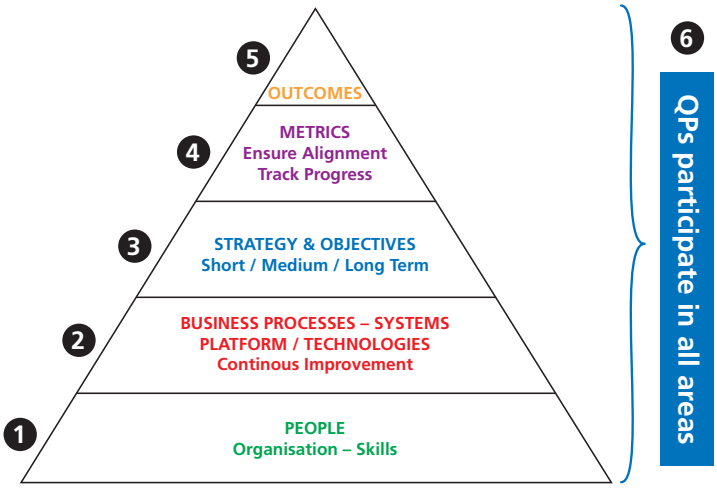


Figure 1

It is essential that the QP understands what drives a typical business in the added value process (see Figure 1) and tries to impact it in all the key elements. Remember – the QPs are uniquely placed to see the "**outcomes**" and therefore can see the reasons for failure, for loss of efficiency and areas of incremental cost. This knowledge gives each of you tremendous power in the game. Don't forget this.

5. Exercising Influence

We have shown that QPs can seriously influence the organization's performance; they are qualified and positioned to do this. However, to "influence" requires broader skills. Sometimes, the positioning of the QP in modern global organizations is complex and this factor has to be managed, particularly within global matrix structures. See Figure 2 for the key areas of interface of a modern QP within the organization.

Duties of QP – Key Interfaces

- To be able to release according to marketing authorization
- Link to regulatory
- Link to change control
- Link to operations
  - ➢ Relationship with production
- Globalization Multisite – manufacturing
  - ➢ Complex supply chains
- External Suppliers
- What must you do yourself?
  - ➢ What do you delegate/take on trust/what needs to be contractual?
- Getting the balance right
  - ➢ You/the company/your colleagues

Figure 2

Understanding, and explaining within the organization, that compliance is a dynamic process, reflecting "current" GMPs and "state of the art" technologies with respect to processing and testing, is also key. Basing decisions on the fact that a product "meets spec", when that product was registered several years ago, is a sure road to disaster for the organization and the QP. Always try to avoid this way of thinking!

6. Maintaining Confidence

QPs can be "influencers" or "blockers." Blockers are those individuals who effectively spectate from the sidelines and act in judgment on the organization. They are incapable of making risk based decisions; they apply authority before influence, destroy organizational confidence and ultimately the performance of the business.

Clearly, having the legal responsibility for product release is onerous and needs to be taken seriously. However, protecting the business from risk by influencing the business processes via personal engagement and respect for the abilities, contributions and motivations of colleagues is far more effective in the long term.

The ability to "fix things on the run" is also essential to maintain confidence in times of crisis.

Consulting and sharing with colleagues is key here – not the "nobody understands me" or the very precious and emotional "I'm legally responsible" attitude we sometimes see. It just doesn't work for the long term.

As QPs you must ensure that your role is understood and respected throughout the organization. This is essential to gain maximum fulfilment and added value from your career. If you really take time to understand your organization, you will find experienced individuals with whom you can share the problems and who respect your position. From my experience that certainly is the case in all large companies.

Make sure you are an influencer and not a blocker!

7. Conclusion

The experience and knowledge I gained in the early part of my career as a QP has given me the platform to do my job well and achieve my personal career ambitions. I'm still a Quality professional at heart and proudly display my certificate as a Fellow of the Charted Institute of Quality! You can achieve the same. As I've already said, you are uniquely positioned in your organization to measure the key outcomes of the business. Finished product release is the final step in the added value process. It gives you tremendous leverage to improve business performance. Use this to influence to the maximum.

Remember what all senior managers really want from their organizations is **"to sleep well at night."**

So, do your very best to give them that peace of mind. I can guarantee it will be recognized and rewarded.

Good luck!

Congratulations to:

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

Helen Brannan, Astex Therapeutics Ltd; **Ruth Buchanan,** GlaxoSmithKline; **Tim Dickinson,** Galpharm International Ltd; **Treena Edwards,** Eli Lilly & Co Ltd; **Dawn Harrison,** Novartis Consumer Health; **Mark Hinton,** Surepharm Services Ltd; **Kate Krachai,** Britannia Pharmaceuticals Ltd; **Meriam Lindsay,** Protherics UK Ltd; **Tony Pinney,** Cardinal Health; **Breda Quinn,** Reckitt Benckiser Health (UK) Ltd; **Simon Tanner,** Actavis (UK) Ltd.

Industry News

EU News

Draft Revision of Annex 2: Manufacture of Biological Medicinal Products for Human Use

Well intentioned but flawed!

In July 2007 the GMDP Inspectors Working Group agreed the wording for a proposed revision of Annex 2. It was released for public consultation in September.

A revision is long overdue – since its original publication many changes have taken place…

- The breadth of regulated biological products has increased markedly, requiring the inclusion of guidance for these products.
- Part II of EudraLex Volume 4 (GMP for active substances) has been published and this provides guidance for the manufacture and control of bulk biologicals – especially in chapter 18.
- The recently agreed regulation on advanced therapies (Regulation 1394/2007) requires specific guidelines for these products.

The structure of the proposed Annex is much changed. In particular, the body of the guidance found in the current Annex has been placed in Part A: General Guidance. A completely new section, Part B: Specific Guidance on Selected Product Types, has been added to provide, as the title suggests, specific guidelines for allergen products, animal immunosera products, vaccines, recombinant products, monoclonal antibodies, gene therapy products, transgenic products and those produced by tissue engineering.

The guidance to be found in Part A is very similar to that in the current Annex, but several important changes have been proposed, including the following…

- Previous guidance on the requirement for facility dedication and/or campaign working for certain kinds of bacteria (notably spore formers) has been replaced by a statement that the need for dedication or campaigning should be determined by a documented risk assessment.

  This is logical as the previous guidance had relevance only for vaccines manufacturers. It is somewhat surprising, though, that it has not been transposed to the Vaccines section of Part B.

- Heavy emphasis is placed on sterility and sterilisation throughout the process, which is rather surprising when one considers that many biological products are subject to sterilisation immediately before filling into the final container. Specific guidance includes…

  9…"Where aseptic processes are used (e.g. inoculation), control measures should be put in place following a documented risk assessment utilising the principles in Annex 1."

  36…"Where sterilisation of starting materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation and filtration). The integrity of any filters used in such sterilisation steps must be assured. Given that the risk and consequences of contamination to the product is the same irrespective of the stage of manufacture, the preparation of solutions and buffers should comply with the requirements of Annex 1."

The biologicals industry would be well advised to challenge these proposals, as they seem to be based upon a false premise; namely that the risk and consequences of contamination to the product are the same irrespective of the stage of manufacture. The consequences of microbiological contamination at cultivation and harvest, when the immediate subsequent steps are non-sterile downstream processing, are **not** the same as those for contamination of the sterilised bulk product during aseptic filling into final containers, nor should they be considered to be. Most important is risk to the **patient**, which is not the same as risk to the product.

If these proposals are not challenged, manufacturers may find they are asked to carry out all so-called aseptic operations in a localised Grade A environment with Grade B background, be required to integrity test all filters (including gas filters on fermenters) before and after each use, and carry out process simulations to confirm the microbiological integrity of these stages (when in many cases each production run is a media fill in its own right!).

It is further proposed that the integrity of containers used to store intermediate products must be validated. It does not state that this validation must be supplemented by subsequent confirmation of integrity on an ongoing basis, but this is a probable additional expectation.

As stated earlier, Part B is totally new and should be read carefully by anyone involved in the manufacture and control of the specific product types covered. At the time of circulation, guidance for tissue engineered products was still in preparation.

In conclusion, the proposed revision of Annex 2 is a generally helpful document but is let down by a perception of risk which focuses on product rather than patient. It is about time we cut the umbilical cord which links environmental expectations for sterile products with those for early stages of biological API manufacture, rather than strengthen it unnecessarily.

Interested parties have until 14 March 2008 to comment.

New Variations Proposal – Update

On 24 October 2007 the Commission issued a further Public Consultation Paper on the simplification of the Variations process. This included the following:

1. Proposals for the implementation of key concepts coming from ICH Q8, 9 and 10; i.e. design space and continual improvement.

2. The introduction of "Do and Tell" for Type IA variations. Such variations do not require any prior approval and can be implemented any time before notifying the competent authorities.

   Reporting of Type IA variations can be done:
   - On the occasion of an annual report compiling all "Do and Tell" changes made in the last 12 months. If no such changes have been made, no annual report needs to be submitted
   - Forthwith in the case of certain Type IA variations which, mainly for administrative reasons, require immediate notification to the authorities

   With this system, Type IA variations would hence fall within two categories, those subject to the annual reporting system, and those subject to immediate notification.

   The proposal also enables the holder:
   - To combine the submission of a Type IA variation requiring immediate notification with the submission of the annual report, provided the 12 months deadline is respected.
   - To group several Type IA variations to the terms of one or several marketing authorisations, which are notified simultaneously to the same relevant authority, within one single notification.

3. Variations to be Type IB by default; rather than Type II as at present.

4. Other proposals
   - A new process for the classification of variations
   - The ability to group variations

The full text of the Consultation Paper can be found at http://ec.europa.eu/enterprise/pharmaceuticals/varreg/consultation_paper_20071024.pdf

Waiting for ~~Godot~~ *Annex 1*

Several revised or new annexes were promised "by the end of 2007"; Annex 1 on Sterile Product Manufacture and Annex 20 on Quality Risk Management being just two of them. At the time of going to press, none of these had been published.

When the revised Annex 1 is published it will be reviewed in detail during our course "A Practical Interpretation of Annex 1" to be held in Manchester on 23 June 2008.

Similarly, if Annex 20 is released in time it will form a key component of our course "Pharmaceutical Risk Management" to be held in Amsterdam from 3 – 6 March 2008.

UK News

UK MLX 345: Risk-based Inspections

In October 2007 the MHRA published a Consultation Letter, MLX 345, on a "Risk-based Inspection Programme for Good Practice Inspections". This proposes a revised risk-based approach to all of the MHRA's GxP inspections; i.e. Good Manufacturing Practice (GMP), Good Distribution Practice (GDP), Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and Good Pharmacovigilance Practice (GPvP).

This MLX proposes that "on a regular basis companies would submit a corporate compliance statement. This statement would form a significant part of an inspectorate risk profile for the particular company. A self assessment report prepared by the company concerned would add to this profile. A review of a company's profile would be performed by the Inspectorate (inspector risk assessment). The output from this would determine the frequency, duration, scope and breadth of any future inspection of the company's site(s) and this would be fed into the inspection planning process."

The MHRA proposals include two new elements that may be part of the new risk-based inspection programme:

Corporate Compliance Element:
An organisation's willingness to comply with the relevant GxP forms an important part of inspection risk management. Also, how effectively an organisation monitors its compliance will be significant. It is proposed that on an annual basis the MHRA would request from the Chief Executive/most senior officer of an organisation information concerning their position with regard to corporate compliance with relevant regulations and how they will ensure that their organisation will meet these. The Chief Executive/most senior officer will be held accountable for the accuracy and completeness of this information as it will form a major part of the inspectorate risk profile for the company.

Self Assessment Element:
A number of Regulators use the self assessment element in their risk management protocol. Experience with blood compliance reports shows that this approach can be a useful tool which can save time and money for stakeholders. If the self assessment process is used, a self assessment report would need to be submitted to the MHRA on a regular basis. This report would contribute to the risk profile for the company. It is envisaged that the report content and detail required in such self assessment will vary according to the needs of the different GxPs.

Industry News

US News

Proposed Changes to cGMPs

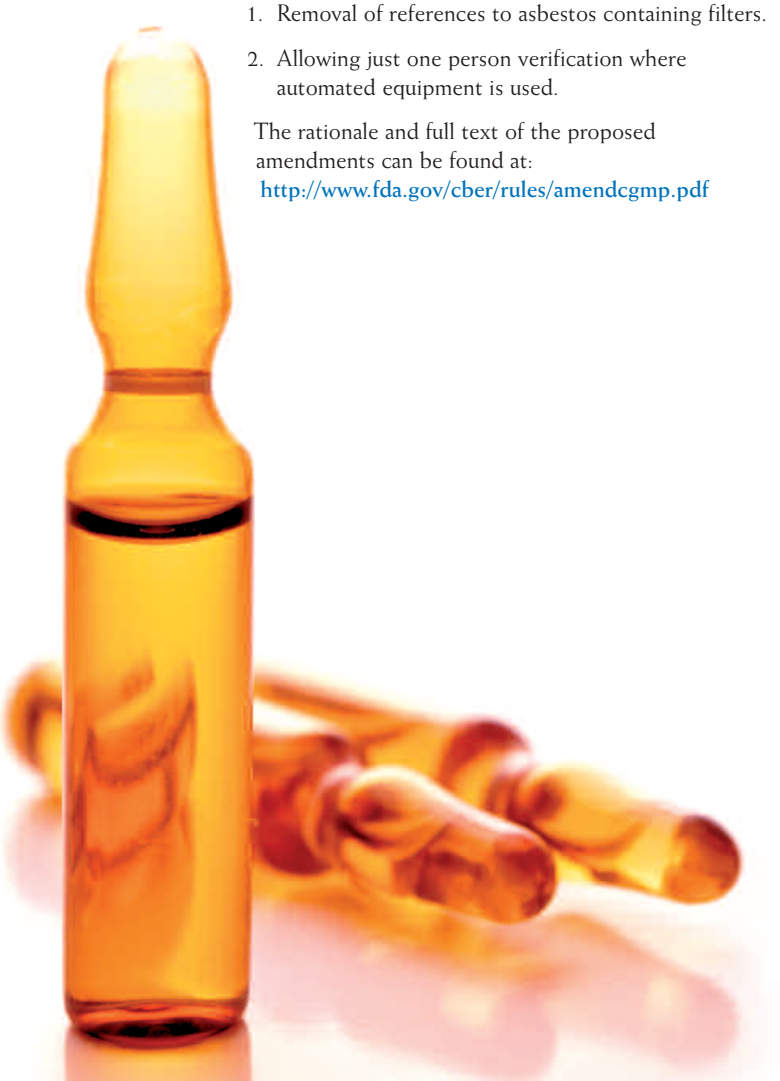
The US Food & Drug Administration (FDA) has published changes to the cGMP Regulations (21 CFR Parts 210, 211) Guide. The modified regulations are intended to align with the 21st Century GMP initiative. With the announcement of the new text the FDA also withdrew the "proposed rule" from 1996.

Comments can be provided until 19 February 2008. If the FDA receives no comments which will prevent the authority from implementing the new content, it will issue an announcement in the Federal Register on 18 March 2008 that will confirm the changes proposed, which will become effective on 17 April 2008.

The proposed changes are not extensive; indeed, there are just two main themes in them:

1. Removal of references to asbestos containing filters.
2. Allowing just one person verification where automated equipment is used.

The rationale and full text of the proposed amendments can be found at:
http://www.fda.gov/cber/rules/amendcgmp.pdf



ICH News

ICH Q8 Revision 1

ICH Q8 (R1), the first revision of Q8, reached Step 2 of the ICH process on 1 November 2007. It is now at Step 3, public consultation in all three ICH regions, and is expected to receive final Step 4 approval at the next ICH meeting in June 2008.

ICH Q8 (R1) provides an Annex to the already approved and implemented Q8 guideline. This Annex shows how the concepts and tools outlined in the parent Q8 document can be put into practice. The Annex elaborates on the elements of pharmaceutical development as:

- Target Product Profile
- Critical Quality Attributes (CQA)
- Linking Material Attributes and Process Parameters to CQAs by Risk Assessment
- Design Space
- Control Strategy
- Product Lifecycle Management and Continual Improvement

The concept of "design space" is elaborated upon with guidance on:

- Selection of Variables
- Defining and Describing a Design Space in a Submission
- Unit Operation Design space(s)
- Relationship of Design Space to Scale and Equipment
- Design Space Versus Proven Acceptable Ranges
- Design Space and Edge of Failure

The final section of ICH Q8 (R1) deals with the submission of pharmaceutical development and related information in the common technical document (CTD) format. There is then a glossary and two appendices.

Appendix 1 of ICH Q8 (R1) contains a useful table that compares the so called "minimal" approach to pharmaceutical development with the "enhanced" quality by design approach.

The full text of the Step 2 version of Q8(R1) can be obtained from the ICH website at www.ich.org

Location, Location, Location...

Kirkbymoorside – Home of DBA

Perhaps the two most common questions we are asked (after "what's the next big thing in GMP?") are:

- Where is Kirkbymoorside?
- Why are you there?

Kirkbymoorside is a small market town on the edge of the beautiful North York Moors (Kirkbymoorside means the church by the side of the moor) approximately midway between the ancient city of York and the North Sea coast.

As for why we are there, the quick answer is because that is where (or very near) David Begg was living when he founded the company in 1986. However, that explains why we started there, but not why we remain there. After all, it would make much more business sense to relocate to a city with an international airport and good road and rail links – none of which apply to Kirkbymoorside.

Hutton-le-Hole

No. We are based in Kirkbymoorside because we want to be! It suits our lifestyle, it provides a good quality of life and environment to raise a family and it offers us much needed respite from the hustle and bustle of airports and city centre hotels. We are proud to be part of a small community, in which we really belong and feel a part of – we use the services of local shops and businesses, we sponsor the annual Kirkbymoorside 10km road race and we support the local schools and charities whenever we can.

Our office, The Georgian House, is near the centre of Kirkbymoorside. Before we bought it, the building was an old people's nursing home which had sadly fallen on hard times. I'm sure that a modern, purpose-built office complex would have suited the needs of our business better, but a 200 year old house gives us the quality of surroundings we like (not to mention a large garden with patio and fruit trees!).

The Kirkbymoorside 10k

Near to Kirkbymoorside are many beautiful villages with strange, old English names like Gillamoor, Slingsby, Helmsley, Hutton-le-Hole and Thornton-le-Dale, and all around us is the beautiful countryside of the North York Moors – great running country!

To go back to those two commonly asked questions…

- Where is Kirkbymoorside?
  In God's own country!
- Why are you there?
  Because we cannot imagine being anywhere else!

Why not come up and see us some time?

DBA People

Kilimanjaro

Mike Halliday tells of his love affair with mountains and his recent ascent to the roof of Africa

Like many people, my early interest in mountains nearly killed me! I remember back in my early 20s setting off to climb snow covered hills without the right training or equipment. Some hours later – wet, cold and trapped under a snow cornice – I vowed to myself, and to whoever was listening, to get the right gear and learn what to do with it. So developed a great love and respect for uplands and mountains and for the outdoors in general.

My trips to these beautiful places have taken me to many mountains and hills across the British Isles and, in the process, I have made some great friends. As I dabbled in rock climbing and winter survival skills courses, I also met some very knowledgeable and skilful guides. Did I become an adrenaline addict? Well maybe – my friends and I celebrated our stag weekends by hanging off cliffs or abseiling 50 metres into a rubber boat in the sea. When I walked down the aisle I was still nursing a few bruises from a recent trip!

In my late 30s I started exploring mountains further afield and somewhat higher and began exploring the Alps. Over a number of years, with a few close friends, I climbed quite a respectable number of peaks over 4000m including Mont Blanc and the Dufourspitze. I really enjoyed the beauty of the places we visited, the sense of achievement and the joy of digging just a bit deeper into physical reserves to reach that elusive summit.

I was delighted therefore when, after a gap of five years in my high altitude climbing due to the arrival of a young family, a good friend, Neil, invited me to join a climb he was organising up Kilimanjaro – at 5895m over a kilometre higher than I'd been before. Who could resist! So started six months of training which involved three to four gym sessions a week, runs of 20-25km most weekends, plus more specific training. Gear was purchased, the trip booked and a long course of vaccinations started. Feeling ready for anything, Neil and I set off to Tanzania to become part of a group of eight climbers with one guide leader, three assistant guides, and 25 cooks, porters and assistant porters. We couldn't have asked for better guides and a better team of climbing companions. The locals were supportive, helpful and sympathetic of our high altitude headaches. We each carried a small pharmacy of medicines and used most on the trip!

After five days walking and camping on Kilimanjaro we arrived at base camp below the summit, from where we would make our final ascent.

Setting off at midnight under a wonderful starlit African sky, we walked, to the encouraging comments of our guides, for the next seven hours until eventually we reached Uhuru peak, the top of Africa! The air was so thin that walking had become a slow painful shuffle. Only by counting each step could we encourage our bodies to keep going. With temperatures of -20°C and a bitter wind, the summit was not a place to linger and after the obligatory summit photos we turned and scree ran our way to base camp an hour or two later.

Celebrations had to wait until we walked out of the national park and made our way through rainforests and coffee plantations back to the hotel. After it was all over, we were left with a great sense of achievement and total respect for our local support, who worked selflessly for our success.

On return back to the UK everyone asked, "what next?" with suggestions like Everest base camp! For me, I think the next big challenge is to help my two young sons to learn how to love and respect high places and to avoid making all those mistakes I made! If all goes well, maybe I will climb Kilimanjaro again, but this time with my boys. Perhaps to celebrate my 60th?

In the next DBA Journal

Industry News: As ever, we search for regulatory changes so you don't have to; Tech Talk: The new Annex 1 (we hope!); Location, Location, Location…: The Imperial Riding School Vienna A Renaissance Hotel, Austria; DBA People: We welcome a new face to the team; Forthcoming Courses: A review of our training courses for Summer and Autumn 2008.

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

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