# DBA

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The Journal of David Begg Associates

Issue 4 Autumn 2006

# A Risky Business?

## A Beginner's Guide to Quality Risk Management in Tech Talk.

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# welcome

## Looking Back on 2006

**Mike Bowsher,**
**Managing Partner**
**David Begg**
**Associates**

As we come to the end of 2006, we can look back upon a year of change for the pharmaceutical industry. There have been numerous regulatory changes and proposals from EU and FDA – some of them welcome, others perhaps not so!

2006 will be remembered by many as the year in which Risk Management became "the next big thing" and we all put our minds to how we should incorporate it into our quality systems.

For all of us at David Begg Associates, however, 2006 will be remembered most of all for the new friends we made over the year. Thank you all for attending our courses and using our consultancy services. We hope we were able to provide you with value for money, and perhaps provide a little fun along the way.

### Looking Forward to 2007

You should by now have received our Training Course Programme for 2007. (If you haven't, please contact us and we will send one to you.) We hope you like the range of courses we are offering and the new venues. Let us know what you think – your opinions are important to us.

Talking of your opinions, thank you to everyone who returned our questionnaire. Your comments are really valuable and we will use them to make improvements for the future. In particular, your comments about our website have been very helpful to us. You can expect to see some changes in the near future.

Mike Bowsher

# Tech Talk

With Pete Gough

# A Beginner's Guide to Quality Risk Management (QRM)

Risk is a familiar concept. We take risks all the time. Even the act of driving to work carries some risk. It is important to understand that in life no activity can ever be totally risk free. Some individuals want to experience high risk (exhilaration?) so they take up pastimes such as rock-climbing, free-fall parachuting, or even bungee jumping. Whatever we do we are constantly assessing the risks associated with our activity and controlling them. If we deem them too high we take risk reduction measures to reduce the overall risk. For example, in free-fall parachuting we carry an emergency 'chute just in case the main one fails to open. So none of us are strangers to the process of risk management, we have done it from an early age and before that our parents did it for us. If we did not behave in this way, our lives could be considerably shorter!

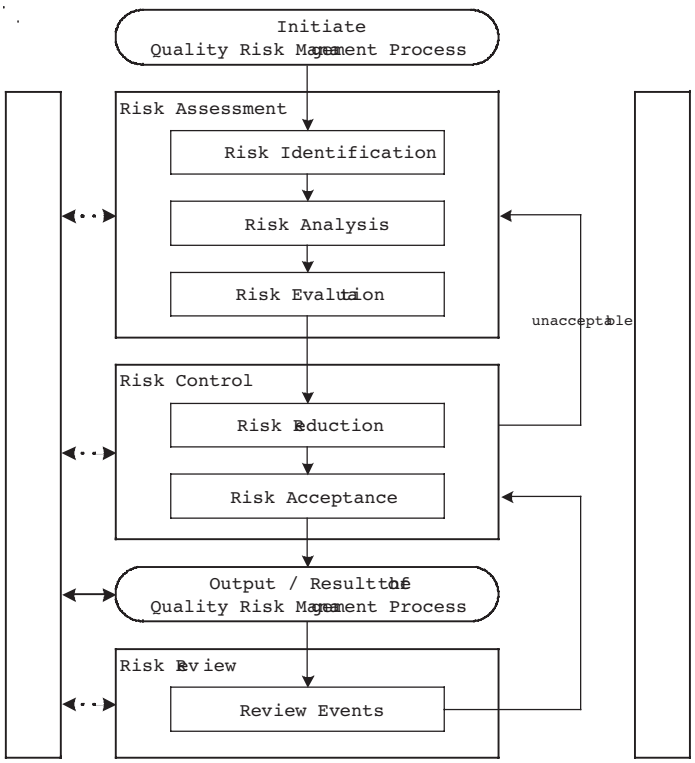


Figure 1: Overview of a typical quality risk management process

The advent of the FDA's 21st century GMP and other initiatives have turned a spotlight on to how we manage quality risks in the pharmaceutical industry. Other industries, including closely related ones like the medical devices and food industries, have adopted a more structured approach to this subject than we have traditionally used. Our approaches to assessing and controlling quality risks have largely been empirical. This is often fine but in more complex or hazardous situations there are a number of very helpful tools and techniques that the pharmaceutical industry has mostly ignored.

ICH Q9 was needed to explain what quality risk management is, how it can be applied to pharmaceuticals and to provide a common language with an agreed process for the pharmaceutical industry and regulators. In many structured risk management models 'risk' is defined as "the combination of the probability of occurrence of harm and the severity of that harm" and this definition is used in Q9. Harm is further defined as "damage to health, including the damage that can occur from loss of product quality or availability".

The ICH Q9 model process for quality risk management is outlined in the diagram (Figure 1).

# Tech talk

The first stage in risk management is Risk Assessment, which is sub-divided into three steps:

Risk identification - identifying potential sources of harm (hazards)

Risk analysis - the estimation of the risk associated with the identified hazards; i.e. the severity and probability of occurrence.

Risk evaluation - compares the estimated risk against your risk threshold to determine the significance of the risk. If the estimated risk is greater than your threshold then it will need to be reduced somehow.

The next stage is Risk Control, which includes the identification of possible Risk Reduction measures and, eventually, Acceptance of the residual risk (which can never be zero).

The final stage is Risk Review, which is the process of reviewing the risk assessment and risk control decisions in the light of experience to identify whether the risks are adequately controlled, and to take any consequent actions.

ICH Q9 provides some details of the tools and techniques commonly used in risk management in Annex 1. The most commonly used tool is Failure Modes and Effects Analysis (FMEA). This is a structured way of assessing the severity of risk and the probability of its occurrence and, often also includes the likelihood of detection. FMEA and other risk management tools allow relative risks to be estimated so that you can prioritise your inevitably finite resources to address the higher ones first. It also allows us to determine those areas where no action is required because the residual risk is acceptable.

Now that we have ICH Q9 approved and being put into effect in the ICH regions it is important for industry to have a strategy for implementing structured QRM. Six important rules for this implementation are:

1. Make sure you have sufficient expert knowledge to be able to assess risks.
2. Ensure that your organisation is aware of ICH Q9 and the opportunity that it affords. A significant amount of education is required here, both in industry and regulatory agencies.
3. Encourage an open, risk aware culture.
4. Keep quality risk management SIMPLE (it is an essentially straightforward concept but as an industry we have a tendency to over-complicate).
5. Integrate QRM with your existing Quality Systems.
6. Be open to new ways of thinking.

*We will be hosting a four day training course entitled "Pharmaceutical Quality Risk Management" from 5 to 8 March 2006 at the Marriott Hotel, Amsterdam. Why not come along and learn how to apply risk management to your operations in the vibrant setting of Holland's capital?*

# Parting is such sweet sorrow

23 June 2006 saw the end of QP module twelve, and so marked the end of the eighth series of our QP training course. Eight series covering eighteen years and hundreds of delegates; many close contacts, friends and even colleagues have come from those ranks.

We are often told by these delegates that one of the key benefits of the David Begg Associates QP training programmes is the opportunity to network with so many fellow students over the courses. The size and duration of the training courses do encourage delegates in getting to know one another and help with the vital networking. To provide another networking opportunity plus mark the end of series nine, I was delighted to be able to offer the delegates and a few special guests a course dinner in one of York's finest buildings, the Merchant Adventurers Hall, which dates from 1357. The location was stunning; we took pre-dinner drinks in the medieval cellars and our meal in the splendid grand hall. The Hungarian/Austrian contingent took me by surprise by kindly providing a special pre-dinner drink of Schnapps.

Entertainment included sleight of hand and stand up comedy from Tony Stevens. Tony got a great reception from the audience, no easy feat with attendees from over ten different countries – QPs really are a tough audience for any magician!

To mark the fact that a group of our "Core" delegates were finishing on that particular module, Stella, our QP course administrator, had organised a course photographer to capture some souvenir shots of the evening with individual photos sent on to the leavers. I thought some of their friends would like a reminder of the event through the medium of this Journal and so I have included some general photos of the evening.

It is always a mixed emotion to see delegates leave at the end of a two year course; sad to say goodbye, but also proud to see these highly motivated and enthusiastic "Technical Leaders" going out to take control of the Pharmaceutical Industry of the future. Over the series many of the delegates have proven themselves to be the leaders of tomorrow – the future of our industry really is in their hands!

## Calling All Former QP Trainees

Over the years we have been asked on many occasions to organise some kind of QP reunion event for former students. Well, we've finally got round to it!

So if you have completed four or more QP training courses with David Begg Associates, try to hold 12 and 13 July 2007 for an event to be based in York - a QP reunion, update, workshop and networking event.

This is your opportunity to re-establish old friendships, keep up to date with current QP "hot topics" and, yes, have a fun time in a city which no doubt holds many memories for you.

*If you were a core delegate on series one to five, do send me an e-mail at QP@david-begg-associates.com to ensure that our records of your contact details are up to date. I have been assured that records since series six are fully backed up and available.*

# Forthcoming Courses

## What's planned for the next six months, Nov 2006 – Mar 2007

### Medicinal Chemistry and Therapeutics
#### Qualified Person & Professional Development Training

**Hilton Hotel, York, UK**
**20 – 24 November 2006**

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

**Course Fee £2,800.00 Plus VAT**

### A-Z of Pharmaceutical Water Systems

**Marriott Victoria & Albert Hotel, Manchester, UK**
**27 – 30 November 2006**

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

**Course Fee £1,945.00 Plus VAT**


### Pharmaceutical Formulation & Processing, Part1
#### Qualified Person & Professional Development Training

**Hilton Hotel, York, UK**
**22-26 January 2007**

First part 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 £2800.00 Plus VAT**

### Risk-Based Decision Making in Sterile Products Manufacture

**Clontarf Castle Hotel, Dublin, Ireland**
**29 January – 1 February 2007**

How to use modern risk assessment 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 £2375.00**

### Ongoing Stability Testing

**Manchester Airport Marriott Hotel, UK**
**6 February 2007**

Chapter 6 of the EU GMP guide has been changed to include a requirement to carry out ongoing stability testing of all medicinal products. This course will provide you with all the information you need to put in place a compliant cost-effective stability testing programme for your products.

**Course Fee £630.00 Plus VAT**

### Product Quality Reviews

**Manchester Airport Marriott Hotel, UK**
**7 February 2007**

Chapter 1 of the EU GMP guide has been changed to include a requirement to carry out periodic reviews of all medicinal products. This course will provide you with clear guidance on what to do to comply with this legislation

**Course Fee £630.00 Plus VAT**

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

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## API and Excipient Supplier Assurance

**Maryborough House Hotel, Cork, Ireland**
**19-22 February 2007**

This course will provide you with essential guidance on how to select, audit, approve and manage the performance of your API and excipient suppliers to meet current EU and FDA expectations.

**Course Fee £2240.00**

## Cleaning Validation

**Manchester Airport Marriott Hotel, UK**
**27-28 February 2007**

This ever-popular course will provide you with what you need to know 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 £1195.00 Plus VAT**

## Pharmaceutical Risk Management

**Marriott Hotel, Amsterdam, The Netherlands**
**5 - 8 March 2007**

Pharmaceutical risk management is the latest "hot topic" in GMP! The FDA have stated that they will use risk assessment in their inspections and expect manufacturers to adopt risk-based quality systems. Furthermore, adoption of ICHQ9, "Pharmaceutical Risk Management" will make it an international GMP expectation. Come and learn what exactly is expected and how to apply risk management techniques to your quality operations.

Our very first course in Amsterdam!

**Course Fee: £2375.00**

## Pharmaceutical Formulation & Processing Part 2, Qualified Person & Professional Development Training

**Marriott Hotel, York, UK**
**12 - 16 March 2007**

Second part of this 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 £2800.00 Plus VAT**

## Free Seminar Qualified Person & Professional Development Training

**Marriott Hotel, York, UK**
**13 March 2007**

Interested in becoming a QP? Why not attend this free seminar to find out more about what we can offer. Learn about what is required to become a QP and see one of our training modules in action.

## Quality Management Systems

**Marriott Victoria & Albert Hotel, Manchester, UK**
**19 - 22 March 2007**

This brand new course will provide you with all you need to know to design, implement, monitor and maintain a cost-effective quality management system to current international regulatory requirements. Whether you are a young, start-up company or a global pharmaceutical giant, this course is for you!

**Course Fee: £2065.00 Plus VAT**

## Practical Aspects of Pharmaceutical Validation

**Marriott Victoria & Albert Hotel, Manchester, UK**
**26 - 29 March 2007**

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 sterile products, computer systems and many more will be covered.

**Course Fee: £2065.00 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**

# Industry News

# EU News

## More Work for the QP!

In June 2006, the EC Commission published revised guidelines on dossier requirements for Type 1A and 1B notifications. These guidelines, to be found in Volume 2C of Eudralex, introduce additional demands of the QP!

As you may be aware, Directive 2004/27/EC brought in the requirement for the QP to confirm that active ingredients used in the manufacture of medicinal products are produced in accordance with GMP, as described in Part 2 of Eudralex Volume 4. These revised guidelines now make it a requirement for a QP of the marketing authorisation holder to certify in writing that active ingredients are manufactured to GMP when reporting Type 1A or 1B variations to the marketing authorisation that pertain to the Active Ingredient Manufacture. Such changes include, for example…

- Change in site for part or all of the API manufacturing process
- Change to location of quality control and batch release
- Change to different manufacturer or a different supplier of starting materials, intermediates or reagents in API manufacture if no Certificate of Suitability is available
- Submission of a new or updated Certificate of Suitability

Where does the QP find the time to carry out all his/her duties effectively?

*These and other issues will be covered in our new training course "API and Excipient Supplier Assurance" to be held in Cork, Ireland, from 19 to 22 February 2007.*

## Clinical Trials in the European Union: IMPs, NIMPs and Volume 10

The EU has recently consolidated all its regulations and guidance on clinical trials into a new volume of the Eudralex series, Rules Governing Medicinal Products in the European Union.

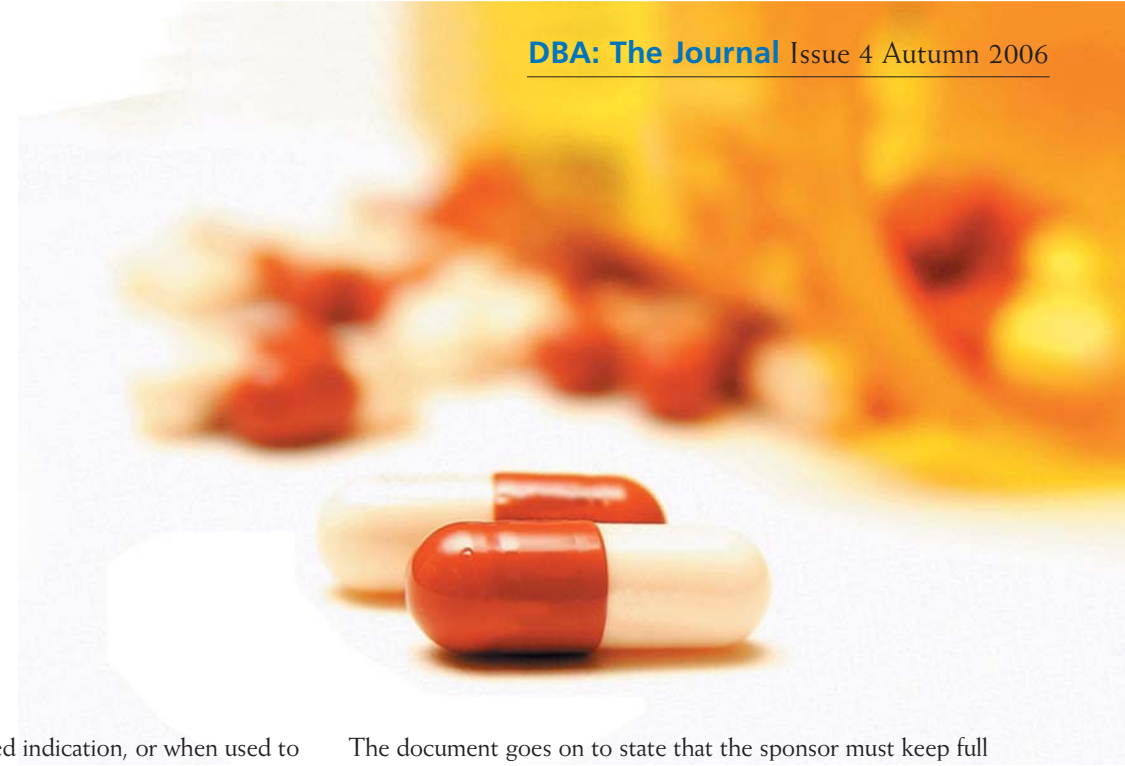
Volume 10 – Clinical Trials – is composed of 6 chapters covering, in order…

- Detailed guidance on how to apply for an authorisation to conduct a clinical trial and information about the European clinical trials database (EUDRACT)
- Guidance on the monitoring of clinical trials and pharmacovigilance
- GMP guidance (Annex 13), guidance on manufacturing authorisations and information regarding chemical and pharmaceutical quality requirements
- General information, including recommendations on the content of the trial master file and guidance on Good Clinical Practice
- All the relevant legislation for clinical trials; Directives 2001/20/EC, 2005/28/EC and 2003/94/EC.

One of the documents included in Chapter 5 (Additional Information) of Volume 10 is a recently published definition of investigational medicinal products (IMPs) and in particular, non investigational medicinal products (NIMPs).

An IMP is defined as…

"a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised



form, or when used for an unauthorised indication, or when used to gain further information about the authorised form."

This definition covers the test substance, the reference substance (active comparator) and placebo.

However, it is sometimes necessary to supply products which are not themselves the object of investigation in the trial, but are supplied to support the trial or as rescue medicines. These are called non investigational medicinal products (NIMPs)

Examples of NIMPs include…

- Rescue medication, provided to assist the patient if the effect of the IMP is too little or too great and is likely to cause patient harm, or to manage an emergency situation.
- Challenge agents, usually given to invoke a specific physiological response so that the effect of the IMP can be assessed.
- Medicines used to assess primary end-points, such as radiopharmaceuticals used to assess organ function. Usually, the test is performed at the beginning of the trial and at the end in order to determine improvement.
- Concomitant medicines, which are simultaneously prescribed to patients suffering from the specific disorder to achieve relief of symptoms.

The document states that, wherever possible, NIMPs used in a trial should have a marketing authorisation in the Member State(s) where the trial is to be performed. If this is impossible, then the next best would be to use a medicine that carries a marketing authorisation in another Member State. In exceptional circumstances, a NIMP with no marketing authorisation may need to be used. Under such circumstances, although the product does not fall under the definition of an IMP, it may be treated as an IMP by some Member States under the terms of the clinical trial authorisation and thus require, amongst other things, QP certification.

The document goes on to state that the sponsor must keep full traceability records of NIMPs, must look for and report significant adverse reactions to NIMPs, and include NIMPs in all annual safety reports.

For full details of Volume 10, Clinical Trials, visit the Eudralex website, http://europa.eu/enterprise/pharmaceuticals/eudralex/index.htm, or save time by visiting "Useful Links" on our website.

# ICH News

ICH Q4B seeks to remove some of the irritating differences in pharmacopoeial testing.

Have you ever been frustrated by the necessity to carry out three different tests or apply three different acceptance criteria to show compliance with the requirement of the United States and the European Union?

If you have, then you will be pleased to hear that ICH intends to do something about this by preparing a consensus guideline ICHQ4B, Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC).

# Industry News

The intention is to gain broad acceptance for harmonised test methods and/or acceptance criteria for a number of common requirements such as…

- Dissolution
- Disintegration
- Uniformity of content
- Uniformity of mass
- Extractable volume
- Particulate matter
- Sterility
- Microbiological quality
- Bacterial endotoxins
- Sulphated ash/ROI
- Colour

Although in its infancy, this initiative promises to make the lives of registration staff and analysts a whole lot easier in the future!

## ICHQ10 – An Update

Following our article on ICHQ10 in the last edition of the Journal, some people seem to have gained the impression that, when adopted, ICHQ10 will replace the EU GMP guide, 21 CFR Part 211 and Japanese GMP regulations. This is most definitely not the case!

ICHQ10, the title of which is now "Pharmaceutical Quality Systems", is designed to augment, not replace, existing GMPs with modern quality system elements for pharmaceutical manufacture. It will describe "a model for an effective quality system needed to establish and maintain a state of control that can ensure the realisation of a quality drug product and facilitate continual improvement over the product life cycle".

A first draft of the guideline is nearing completion and covers topics such as key elements of a Pharmaceutical Quality System, management responsibilities, and continual improvement requirements, both for the system and for product quality.

It is expected that ICHQ10 will reach step 2 of the ICH process in late 2006 or in 2007.

ICHQ10 promises to be a key document – watch this space!

*This and other issues associated with the design, implementation, operation and maintenance of an effective, compliant Quality Management System will be covered in our new training course "Quality Management Systems", to be held in Manchester, UK from 19 to 22 March 2007*

## ICH PUBLISH Q9 BRIEFING PACK

ICH has recently published a "briefing pack" to support guideline Q9 "Quality Risk Management".

The pack consists of documents and slide presentations covering risk management tools (FMEA, HACCP, FTA etc) and how risk management principles may be applied to activities such as development, facilities, materials management and many others.

The briefing pack can be found on the ICH website, www.ich.org, or via the "Useful Links" sector of our website.

*Pete Gough, who contributed to ICHQ9 and the briefing pack, will be leading our 4 day training course "Pharmaceutical Risk Management", to be held in Amsterdam, The Netherlands, from 5 to 8 March 2007.*

# Location, Location, Location...

## The Clontarf Castle Hotel, Dublin.

## One of our personal favourites!

A 30 minute taxi ride takes you from Dublin airport to one of our favourite course hotels – the Clontarf Castle.

Built around the remains of a real castle, the hotel provides excellent accommodation, great facilities for a conference and a warm welcome that is difficult to better!

Extensively refurbished during the summer of 2006, the hotel provides intimate dining in Templars Bistro as well as casual eating in the more relaxed atmosphere of Templars Bar. If you are interested in working off the calories, there is a well equipped fitness centre, but walkers and joggers are recommended to go 300 metres south of the hotel where they can exercise along the coast of Dublin Bay.
Good as the hotel is, it would be a crime to visit and not go into Dublin city centre. A 15 minute taxi or bus ride brings you to one of the warmest, most welcoming cities in the world! There is great shopping around Grafton Street and the restaurants and bars of the Temple Bar district provide something for everyone.

Overall the Clontarf Castle Hotel is an ideal location for learning and for pleasure!

We shall be holding the following courses at the Clontarf Castle during early 2007:-

Risk-Based Decision Making in Sterile Products Manufacture

- *29 January – 1 February* 2007

Pharmaceutical Good Manufacturing Practice

- *23 – 26 April* 2007

# DBA People

In each Journal we spotlight a member of the DBA team so that you can get to know us better. In this issue it's Peter Smith.

## The Car's The Star!

We all look back fondly to the first car we ever owned – I can still remember the registration number of my first mini, but can't remember the number of my current car – and many of us secretly wish that we could own one just like it again, just for old time's sake. Not only has Peter Smith done just that – he has also turned the car into a TV star!

Peter's first car was a Morris Minor saloon, although he always hankered after the sleeker convertible version. So when an old, dilapidated convertible was offered for sale locally some years ago, Peter jumped at the chance to buy it.

The previous owner had started renovation of the vehicle, but Peter found he had to replace nearly every moving part in order to create his dream car – a good-as-new 1950s Morris Minor convertible.

So good, in fact, that the car (and Peter) were invited to appear in a popular UK Sunday evening TV show, "The Royal", a "soap" set in a Scarborough hospital in the 1960s. "I spent two days rubbing shoulders with the stars whilst waiting for the car's big moment. We "starred" in two episodes," Peter told me.

However, an extra's life is not all fame and fortune – Peter and Morris started work at 7.00am each day and had to sit for several hours waiting for the call from the director. Not everyone's idea of fun, but very definitely worth it. "After insisting that all my family watch every single episode of The Royal, the car was finally spotted – TWICE", Peter says. "I even have the video evidence to prove it."

Peter and his family regularly drive the car around the lanes of North Yorkshire at weekends (weather permitting) and he is rightly proud of his baby. As for Morris, he is currently reading scripts before deciding upon his next screen project!

## Congratulations to:

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

Peter Gannon, GE Healthcare Ltd, UK, Catherine Kay, Merck Sharpe & Dohme Ltd, UK, James Muller, Pfizer Ltd, UK, Dan Pilkington, AstraZeneca Pharmaceuticals, UK.

## In the next DBA Journal.

Industry News as ever, we search for regulatory changes so you don't have to, Tech Talk environmental monitoring…to speciate or not to speciate? That is the question. Location, Location, Location…the Marriott Hotel, Amsterdam, DBA People a profile of Mike Bowsher. Forthcoming Courses – a review of training courses for Spring and Summer 2007.

**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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