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BARQA Annual Conference
Royal Bath Hotel, Bournemouth
1st - 3rd November 2006

Brochure, booking form and programme details available soon

www.barqa.com

We have redesigned the BARQA website with a new look and feel and made it easier to use.

Your membership number and password remains the same, so please have a look around the site and let us know your comments by contacting the editor@barqa.com

Go to the website and win a prize of £50 high street vouchers if you can answer the following question.

How many people are in the Computing Committee picture on the website?
The winner will be independently drawn from all the correct entries received by the 1st of May 2006. Answers should be sent by email to the editor@barqa.com
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Material for publication in QUASAR

Quasar is published 4 times a year and articles can be submitted to Quasar at any time and should be sent initially to the Editor/relevant Sub Editor. The final copy deadlines are as follows:

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Whilst every effort is made to produce and distribute Quasar as early in the month as possible, no guarantee can be given to publish on the first day of the month.

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Welcome to the second edition of the new look QUASAR. We have had some great feedback from you about the new format so I hope you enjoy this issue as much as the last one!

As recent events at Northwick Park Hospital have shown no matter how careful one is, things can go wrong. It is a painful and difficult time at present, but as Lord Winston said recently in defence of the Pharmaceutical Industry: “I think it’s really unfortunate that there might be given an impression that our very ethical drug industry is actually not working according to proper practice because I think on the whole it undoubtedly is.” I am sure lessons will be learnt and such tragedies will be avoided in future.

The theme of this issue is Corrective and Preventive Action (CAPA) as graphically illustrated on the front cover shot of Buncladia petrol terminal. We are delighted to have received some varied and really excellent contributions on this topic, across all the GxPs, from Hanif Patel, Nigel Crossland, Judith Elliott, Stephen Nicholas, Andrew Waddell and Andrew Tipping. As well as all QUASAR’s regular features, Barry Travena’s latest ‘Cornucopia’ is a great read.

There is also the first in a series of articles about MHRA by Bryan Wright. The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency which is responsible for ensuring that medicines and medical devices work and are acceptably safe. Full details of their activities can be found on www.mhra.gov.uk.

In this edition of QUASAR MHRA’s structure and functions are outlined and this will be further explained in the next edition of Quasar. We are all aware of the GXP inspectors and they are an important element of MHRA for enforcing regulations. If you are interested in becoming an inspector please check the BARQA website www.barqa.com.

The next edition’s theme will be Risk Management and we already have a number of contributors lined up. However, if you would like to submit an article for the July issue on this theme or any other topic, please do get in touch with a member of the Publications Committee.

In the January issue of QUASAR (Dear QUASAR) we featured an article on what the past Chairman of BARQA does in his spare time. Unfortunately we did not name the past chairman, so many apologies to Nigel Dent.

Finally do visit the new BARQA website. You could win $50 worth of high street vouchers - so have a go. Check out the new features and let us know what you think of it. We value your comments.

Wishing you all the best and an enjoyable read.

Ramzan Visanji
Dear Colleagues,

So how do you like our new look Quasar? All feedback so far is very positive and I encourage you to provide your honest comments to any member of the Board. That is really the only way we can judge its success and make changes as required. As it is obviously highly pictorial in content, a continuous supply of images is required to maintain its artistic presence.

Does your company’s marketing group have any images which they would be prepared to let us use to illustrate Quasar? or are you a talented photographer who could contribute your own work? The editor would really like to hear from you.

For a theme this quarter, perhaps you would like to hear about some of the topics discussed during our Board meetings.

The Board held its 74th meeting on 19th January in the Novotel at Birmingham Airport and with all members in attendance. No mean feat when everyone is so busy with their day jobs.

I was delighted to welcome five new board members:

- Allison Jack – Chair of Pharmacovigilance Committee
- Vic Edy – Chair of GMP Committee
- Ramzan Visanji – Chair of Animal Health Committee
- Penny Beane – Chair Elect (my successor?)
- David Balles – Treasurer

**New Booklets:** A Trilogy of new guides is now complete and the Publications Committee is working on a decision tree which will help with publishing our outputs in the most effective way.

The guides in question are:

- Good Veterinary Clinical Practice – A Monitor’s Guide
- A Practical Guide to Pharmacovigilance Audits
- A Practical Guide to Pharmacovigilance Regulatory Inspections

**New Web Site:** Congratulations to the Publications Committee, Tony Ward (BARQA Office) and StatusMedia Web Solutions, on the launch of the new BARQA web site. We hope that you find the new site attractive and easy to use. I was fortunate enough to be given a preview and I particularly like the search capability and the fact that I can book flights just a few clicks from the home page.

However, just in case I am biased, I leave you to judge for yourselves.

**Regional Forums:** As you will have seen in the last Quasar, there is a lot of regional activity going on in the British Isles. From interest expressed from other countries viz. Australasia, the Board has agreed in principle to the establishment of regional forums (or should that be fora?) in more distant regions.

**New Member Welcoming Scheme:** Feedback and comments received and gathered by the Membership Needs Working Party were consolidated and the outcome is the Scheme which is launched in this edition of Quasar.

**New Pharmacovigilance Committee:** This is an exciting new component to the BARQA Board and Allison Jack has been working very hard to establish the membership of its committee. There has been a great response to the call for members to serve on the committee – many more than allowed on a BARQA committee. However, I am sure that those who did not make it will be called upon to help move forward in this challenging area. Many thanks for all your enthusiastic support.

**Professional Development:** A new course has been added to the Professional Development prospectus ie. Systems Audit. In today’s world of government agency inspections which tend to focus on a systems approach to assessing compliance, this course will help you understand what is meant by a ‘System,’ how to set up an appropriate monitoring programme and how to establish quality improvement initiatives to prepare for regulatory inspections.

BARQA received an invitation from JSQA to have one of our members deliver a presentation at their annual conference in June 2006. This has been taken up by Rita Hattemer-Apostel who will be sponsored by BARQA for the round trip and whose presentation is to be entitled ‘Comparison of approaches to quality in GCP/GLP and GMP.’

Many thanks to our Japanese colleagues for the kind invitation and to Rita for agreeing to fly the BARQA flag.

Let me finish on two topics which will be discussed at the next Board meeting to be held here in Edinburgh on 20th April.

The first relates to Quality Risk Management – a subject taken up by ICH and published as Q9. Whilst the focus of its content would appear to be GMP and PV area, it was agreed that a BARQA Working Party would be established with Allison Jack ‘volunteering’ to be the Board sponsor.

This is a topic attracting a great deal of interest in the pharmaceutical industry world wide and as such could be relevant to a large percentage of our membership.

The second and final topic for Board discussion which could be considered as the end point of our ‘looking inward, projecting outward’ modernisation programme is ‘strategy for the future.’ Much has been discussed and proposed in the past on this theme but now is the time to decide where do we as BARQA want to be in the future?

Do we have any strategic planners out there? If so, please come forward and be identified.

As always I wish you well and trust you enjoyed the new Quasar and will relish in the new Web Site.

Many thanks for your continued support to BARQA.

Ronnie
I sometimes feel as if I have been working in QA forever! Many years ago I was a founding member of the original Quality Assurance Group. This was a small group of people who were the forerunners of the QA professional that we have nowadays and we grouped together for safety because we were all fighting an uphill battle to convince our managements that GLP was important and should be viewed constructively. The level of resistance needed to be felt to be appreciated. The QAG then became bigger and more professional and eventually transformed itself into BARQA. I have been a member of BARQA ever since, I have spoken at BARQA conferences, I was Chairman of the BARQA GCP Committee for 2 years, and now I am Treasurer.

In 1989 I extended my QA interests to include GCP as well as GLP and, when ICH GCP was being drafted, I found myself on the EU industry committee set up by the European Federation of Pharmaceutical Industry Associations (EFPIA) whose job was to negotiate with the US and Japanese counterparts to make sure that the GCP text ended up with the right wording and coverage for the intended global use of the guideline. I still think about that every time I read something in GCP and wonder what it was intended to mean!

I have worked my whole career in industry as a QA professional covering the introductions of GLP to pre-clinical research in the 1970s and GCP to clinical research in the 1990s. I was Deputy Head of Pre-Clinical QA for Pfizer for 3 years and Head of European CQA for Pfizer for 9 years. During this time I worked in France as well as the UK and so I joined SOFAQ (the French equivalent to BARQA) and I remain a member today.

I left Pfizer in 2003 and now run my own research QA consultancy which specialises in research quality and has clients in the pharmaceutical and cosmetics industries. I provide expertise in research quality and auditing, process quality and improvement, training in GCP and GLP etc.

Consultancy work has its own challenges but I do enjoy the benefits of working from home and being able to manage my diary to good effect. I have a working wife and two children at university and it is especially pleasing to know that I can set aside some time to support them all as necessary and to avoid having to squeeze a thousand things into each weekend. My dogs get more walks too – though I have the impression since I have started working from home that they think I intrude rather on their space! Luckily, consultancy also has its fair share of business travel so they can relax a little when I am away.

Travel (for leisure), wine, and a passion for all things French occupy the rest of my time.
After a first degree in Microbiology, and a PhD in Biochemistry, I took up a post-doc offer in Belgium, and ended up spending six years there, working on interferons. I then joined the University of Berne, in Switzerland. After two years, I moved again, this time to industry in the USA, joining a company, Flow Laboratories, that had just won a US government grant to manufacture interferons.

After three years of this, I came back to the UK manufacturing site for Flow Labs, in Ayrshire. Somehow I was given a product quality investigation to carry out. This fascinated me, and I began a long-term interest in QA and GMP, becoming the Quality Assurance Manager at Flow.

Anyway, after seven years in Scotland, I became Head of Quality at British Biotech. This was a new position, and carried responsibility for the QC department, as well as QA and GMP and GLP compliance. As BB grew, so did my department. Then BB came a major cropper, and I had the intensely difficult task of reducing my department significantly. After a couple of rounds of redundancies, I had had enough. So, I quit, and set myself up as a one man consultancy. That was just over 5 years ago.

and I’m still at it, spending my time mostly giving GMP guidance, mainly to small start-ups; and carrying out audits of manufacturing and analytical contractors.

To help me keep in touch with other QA professionals, I joined BARQA several years ago. One day, I spotted a notice in Quasar seeking new members for the GMP committee. So I applied, was accepted, and at my first meeting was the first to crack when the chairman asked for someone to volunteer as secretary. I then took over as chairman in 2005.

For relaxation, I go walking with my wife (the photograph on the left was taken last year in the Black Forest), go to concerts and the opera (I could bore for England on Handel’s operas), and have recently started a model engineering project to build a small steam locomotive, although at the moment my main products are swarf and scrap.

Vic Edy
CHAIRMAN GMP COMMITTEE & BARQA BOARD MEMBER
Due to the diverse membership of BARQA this article will focus on what the key elements of Corrective and Preventive (CAPA) systems are and not how a CAPA system should be managed as this will vary from organisation to organisation. I also need to clarify that this article is a personal view on what a CAPA system should contain and is in no way reflective of the CAPA system within GlaxoSmithKline.

To ensure we are all on the same page let’s ensure we understand what is meant by Corrective Action and Preventive Action:

**Corrective Action** is an action taken to eliminate the cause of a detected non-compliance or non-conformance.

**Preventive Action** is an action taken to eliminate the cause of a potential non-compliance or non-conformance.

The CAPA system is a key and integral part of any quality system within an organisation since the purpose of the system is to identify, assess, evaluate, implement and monitor solutions to address actual and/or potential non-conformance or non-compliance occurring or re-occurring. The CAPA system is in itself inherently linked to several other quality systems like Audits (internal, external or regulatory agency), Quality Investigations, Customer Complaints, Risk Assessments etc. The CAPA system by its nature is not solely restricted to the quality system as it can equally apply to other areas like Safety, Environmental Health etc. (Also – some organisations generate CAPA on an ad hoc basis).

**PLAN**

The planning of the CAPA starts by understanding the identified potential or actual root cause of the Quality Investigation, Customer Complaint, Audit observation etc. Thus it is essential that the root cause analysis performed to get to the identified potential or actual root cause is fundamentally sound for the CAPA to be truly effective. Once the potential or actual root cause is understood an owner for the CAPA should be identified. In some circumstances if root cause covers several areas of the organisation then a CAPA team may be required to be set up.

The owner (team leader) is accountable for ensuring:

- that the correct and appropriate Corrective and/or Preventive Actions are identified to address the identified potential or actual root cause. There is risk assessment done of implementing the CAPA and actions (safe guards) to manage these risks.

- resource required to implement the CAPA is identified and allocated.
• timeline to complete the CAPA is determined and agreed
• criteria for assessing the effectiveness of the CAPA are identified and defined and the associated alert and actions limits
• Implementation plan is created. This should also include plans of safe guards whilst the CAPA is being implemented to manage any identified and defined risks.
• Implementation of the CAPA
• review of the effectiveness of the CAPA

The CAPA and its associated implementation plan need to be approved by the management of the business impacted by the CAPA(s) and Quality Assurance. The QA approval is to ensure that CAPA(s) will address identified potential or actual root cause and to agree to the timelines for the implementation of the CAPA(s).

DO
The implementation plan should then be followed by individuals identified to perform each of the activities in the plan. The CAPA owner should ensure that the management (normally this would be his or her immediate manager) of the business impacted by the CAPA activities is provided with progress reports.

Any changes to the proposed implementation plan should be approved by QA and the manager of the CAPA owner.

CHECK
At the completion of the CAPA, an independent verification by QA group on the deliverables of the implementation plan should be done. As a result of this review the CAPA can be closed out or not by QA.

A monitoring system should then be implemented to monitor the effectiveness of the CAPA against the pre-defined criteria. It is advisable to have action and alert limits on the criteria so that on reaching the alerts limit defined actions can be taken.

The other most important aspect of CAPA is the review and monitoring of the whole system, better known as Key Performance Indicators (KPIs) for CAPA. This is where an organisation can really enhance its quality culture, performance and compliance or get it terribly wrong. The KPI should be there to identify areas of improvement in the system and identify and remove potential road blocks to getting the CAPA’s completed. Again the identification of what KPIs are needed will depend on the organisation and what it wants to achieve. However, one KPI must be on completion of CAPA. This is where the way in which this particular KPI is used can either enhance compliance and build a quality culture of ownership by each member of staff or be extremely detrimental if not managed well. The purpose of this KPI is to look at the percentage of CAPAs completed on time and the percentage past due dates. The focus on the past due date is to understand why these are past due date and evaluate if any actions can be taken to expedite the closure. The behaviour of management on past due date CAPAs should essentially be around what could be done to expedite closure by either re-prioritising the workload of the individual responsible for the CAPA or providing additional resource. This behaviour will ensure that staff will be more willing to take on responsibility of CAPAs. The KPI should not be used in anyway as a punitive measure against the individual: if it is this could be extremely detrimental to the building of a culture where individuals feel ownership of quality.

These KPIs once identified should be reviewed by the management teams at regular intervals and actions, learning points identified from these reviews should then be acted on.

ACT
The outcomes of the review of the KPI should be used to Act and then Plan the change to the CAPA system. The changes may be with respect to change of the tools used for identifying the root CAPA or training of staff identifying the CAPAs or the KPIs, etc. The actions identified then go through the PDCA cycle again.

Hanif Patel

Hanif is currently the Vice President of Global R&D Quality Assurance and Core Labelling Management for GlaxoSmithKline Research and Development. In this role he leads the QA group providing QA support to Chemical, Biopharmaceutical and Pharmaceutical Development at all GlaxoSmithKline R&D sites and also the Global Core Labelling Management group providing the support for the company position with respect to prescribing and patient information for all GSK products.

Hanif was a past member of the BARQA Board and Chairman member of the GMP Committee.
CAPA - It’s as easy as ABC

For the Corrective And Preventive Action (CAPA) system to be effective it should involve all disciplines, not just the auditor.

To understand everyone’s role, the CAPA process should include a clear strategy involving distinct stages, describing where responsibility passes from one party to another and defining overall responsibility. Most importantly, senior management should sponsor and demonstrate ownership of the whole CAPA process so that a clear message is sent to all involved that CAPA is critical to the overall success of the business.

In addition to policy and system definitions, it is also essential that records of the CAPA activities are maintained. This not only provides Management with the confidence that the system is operating, but also supplies data that can be used as a performance monitoring tool. If the same causes are repeatedly identified, Management can focus attention on this area for maximum benefit.

So what role can the auditor play in this process?

If a clearly defined strategy is missing the auditor can demonstrate how their activities contribute to the overall process and encourage all other parties to adopt a similar approach.

For ease of reference let us refer to the process as P.R.I.M.A.T.E.

Purpose
Firstly, the auditor should ensure that they clearly understand the purpose of the audit. When the purpose is to validate compliance, any opportunities for improvement identified during the audit will be outside the scope of the audit.

The audit scope and plan will also contain lots of other useful information, including responsibilities at various stages of the audited activities and will therefore provide guide to when and where responsibilities begin and end.

To achieve a successful outcome, i.e. ensure or re-establish compliance, it is essential to adopt a team based approach. Experience has shown that without this subsequent events can degenerate into a battle between the auditor and auditee and rarely result in any real benefit to the organisation.

Report
The audit report should focus on the most important issues. Non-conformities should be reported in a clear and concise manner, with the most serious being differentiated from the more trivial. The auditor can assist in this process by (a) openly discussing concerns in the closing meeting with the auditee, and also with the audit client and (b) grouping non-conformities into a small number of critical categories so that the audit client, or management for an internal audit, receives a clear picture of the activities requiring urgent attention.

Non-conformity is non-fulfilment of a requirement. Where an audit finding cannot be clearly identified as a non-conformity, it could be reported as a comment or an observation, providing the audit recipient an opportunity to investigate further and carry out preventive action(s).

Corrective Action is action to eliminate the cause(s) of a detected non-conformity. It is taken to prevent recurrence of the non-conformity.

Preventive Action is action to eliminate the cause(s) of a potential non-conformity. It is taken to prevent occurrence of a non-conformity.

Identify
Once the audit findings have been reported the audit client can prioritise their response and focus on the issues that provide the best return.

In some cases this might be an immediate action (correction) and in another it may involve a detailed investigation that promotes a change or improvement to a system (corrective action).
Whatever the outcome, it is essential that in order to gain a full understanding of the problem, the audit client identifies the key processes associated with the audit findings and assigns appropriate responsibilities and timelines for action.

The auditor can re-enforce this expectation during discussions, and/or provide or agree a template format for the response if none exists.

**Map**
To gain a clear understanding of what happened during a particular activity and how the event occurred it is important to map key processes and causal factors. This is most effectively achieved if an external party that is independent of its outcome facilitates the process.

The auditor can play an important role, if asked to, by acting as the impartial facilitator in the investigation to find the cause of system failure.

**Analyse**
Once the key processes and causal factors have been mapped, the root cause(s), i.e. the basic cause(s) for which effective actions for preventing recurrence/occurrence can be taken, can be identified. Taking time to determine the root cause of the problem will prevent the wrong decisions being made for corrective/preventive action, which is so often the cause of recurring non-conformities.

**Take Action**
Only after the root cause has been determined and agreed, is it sensible to implement action to address the non-conformity or observation. Acting too soon is ineffective, costly and generates an overall lack of confidence in the CAPA process.

When subsequent actions are based upon a detailed investigation of root cause, there is significantly more confidence that the effort and cost involved in implementing change will be worthwhile.

To ensure that there is agreement on the effectiveness of corrective/preventive actions participants should establish measures (sometimes metrics) that will prove the effectiveness and/or efficiency of proposed changes. Only after these measures have proven the suitability of the corrective/preventive action can the audit findings be satisfactorily closed.

**Evaluate**
To ensure that the corrective/preventive action has been successful, someone needs to evaluate its effectiveness. If measures have been included as part of the proposed solution they can be used.

Where metrics clearly indicate that recurrence of a non-conformity has been eliminated the audit finding can be safely closed.

The auditor should consider carefully the benefit of performing a follow-up audit, due to the cost and disruption this can entail. There are often good reasons for accepting objective evidence or even the word of the system owner that the problem has been permanently solved. At the next scheduled audit of the system, the auditor can select a corrective action and assess its continued effectiveness. This also provides a chance to audit the corrective/preventive action process.

**Conclusion**
It is accepted that P.R.I.M.A.T.E. is a time consuming process, so it should only be applied to those audit findings that warrant such a detailed investigation. The auditor can assist in ensuring that P.R.I.M.A.T.E. is applied to the highest order problems by focusing on the non-conformities that pose the greatest risk (or provide the greatest value) to the organisation, when compiling their audit report.

Definitions and terminology used are from:
- BS EN ISO 19011:2002 - Guidelines for Quality and/or Environmental Management Systems Auditing
Investigating the reasons for (adverse) audit findings

In search of the corrective and preventive actions in the wake of clinical research audits

In order to address correction and preventive action strategies (CAPA) in GXP a good starting point would be the underlying systems associated with adverse audit findings.

From many hundreds of audits I have performed, the following examples are chosen of adverse (and some could say unusual) findings arising from various clinical research settings in the UK and international sites (covering Europe, Asia and Africa):

- **Product labelling in clinical bioequivalence laboratory**
  The product label was in a foreign language and could not be read by anyone, including the research site’s pharmacist. Shipment records also failed to unambiguously identify the product except by batch number and thus could not be cross-referenced to the label. As batch numbers are not unique across products, the site pharmacist had thus released the product to the investigator without positively confirming the product’s identity. In addition, product information for this bioequivalence study had not been provided by the sponsor.

The sponsor was reminded of its obligations regarding the two product deficiencies found at site. The site pharmacist was also warned of the seriousness of this mistake and to always ensure documented and unambiguous confirmation of investigational product identity is obtained before release to the investigator.

- **IMP storage temperature at hospital site**
  Temperature charts revealed that drugs had been stored at high temperatures since arrival at the hospital. The monitor had failed to notice this and thus the problem had not been brought to the attention of site personnel or the CRO/laboratory project management or the sponsor.

  Temperature charts in two other hospitals were found to be extraordinarily constant, showing absolutely no variation over an 8 week period. In one hospital the person responsible for reading the thermometer did not understand how the thermometer worked. The thermometer in the second hospital was broken.

In both these cases, the monitor could have noticed and queried the unbelievable records and tried to discover an explanation and thus rectify the situation.

- **Investigator’s source records in Phase II clinical trial**
  The validity of computerised medical record systems at site had not been confirmed, despite the CRO having an SOP for checking this, which the monitors should have followed.

  Validation was confirmed and thus correction achieved during the audit. Addressing preventive action, the CRO was recommended to ensure that monitors carry out all aspects of their assigned tasks, especially those during pre-trial site assessment, which involves more than just ticking boxes.

- **Independent clinical archives deficiencies**
  Night-time security at one site was inadequate and storage temperature and humidity at a second site were grossly unsuitable for document storage. There was also evidence of environmental records having been fabricated.

- **Temperature monitoring equipment**
  In search of the corrective and preventive actions in the wake of clinical research audits
• **Unfit for purpose consent forms**
  During the audit of a paediatric trial it was not possible to confirm that a valid consent form existed for each subject as the form did not ask for the subject’s name or signature. This problem arose as a result of confusion regarding confidentiality of paediatric trial subjects on the part of the local ethics committee who were responsible for design of the form. In order to correct this deficiency, the monitor and local project management, who were apparently aware of the problem, could have asked the investigator to compile a list of the names of parents/guardians signing the forms and by cross referencing this with the names of the subjects on the screening/recruitment records and simply recording the subject’s identification numbers as well as project identification onto the completed consent forms. If the problem had been detected before site initiation, the investigator could have been asked to request correction from the Ethics Committee, of the deficient consent form.

• **Un-calibrated weighing apparatus at hospital site**
  During an obesity trial, the monitor rightly questioned the reliability of bathroom scales that the investigator intended to use. The investigator was not happy to be asked to use a set of standard weights to check the accuracy of the scales and incredibly dismissed the monitor. The audit later confirmed the site was generally satisfactory except for the earlier conflict with the monitor. It was concluded that the problem could have been avoided if the site had been adequately checked before the trial start date and the need for accurate weighing apparatus had been courteously explained to the investigator.

It is probably true to say that most of these audit findings are uncomplicated and could easily have been prevented if adequate consideration and common sense had been afforded to the various causative elements at the outset.

**Addressing CAPA strategies:** raising monitoring performance and improving project management QA awareness were recommended in the relevant audit reports. Monitors should fulfil all of their responsibilities and project management should not fail to keep abreast of the visit reports and data quality. The pharmacist who released unknown product should have been requested to undergo revision training with emphasis on safety responsibilities and the sponsor needed to review its product release procedures. With drug storage temperatures, it would have been wise to confirm that everyone knew how to read thermometers and the monitor didn’t just blindly check study records. Completion of valid consent forms is an essential foundation procedure and shouldn’t be left to trust. The deficient archives were concluded to be the result of deliberate and improper management practices and were unlikely to have occurred as a result of innocent mistakes. Prevention here would involve finding a better supplier.

**Simply completing tick-box forms without thought is not adequate.** Organisations that rightly apply the necessary quality standards, implement associated policies and invest time and effort in training personnel can often avoid such problems. One should also appreciate that experience teaches us to anticipate problems before they occur.

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**Nigel J. Crossland**

**BSc, FRQA, FICR**

Nigel is founder of the Crossland Consultancy, specialising in QA support in clinical research. His experience in pharmaceutical research is extensive and includes the performance of more than 700 GXP audits (incl. >90 laboratory audits) and many training programmes in over 20 countries covering 4 continents. He is a strong advocate in the belief that it is not people who are audited, but operational systems. Nigel has fellowship level membership of both BARQA and the Institute of Clinical Research.

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Corrective and Preventive Action (CAPA)

Introduction
Corrective Action and Preventive Action are, in many people’s minds, associated with the action taken to correct a non-conformance and to prevent a repeat of that non-conformance, respectively. But CAPA is much more than that, it is a process in its own right and goes far beyond the definitions given in the first sentence.

In fact the terminology is a good place to start since the actions associated with Corrective Action and Preventive Action have been re-defined and a new term introduced. Corrective Action is the action taken to eliminate the cause of an existing non-conformance, defect or other undesirable situation in order to prevent recurrence. Preventive Action is the action taken to eliminate the cause of a potential non-conformity, defect or other undesirable situation in order to prevent occurrence. Correction or Containment is the process of repairing, re-working or fixing a problem that relates to the disposition of an existing non-conformity.

Non-Conformances
The first encounter many people will have with the CAPA process is through some form of non-conformance. A non-conformance occurs when a non-compliance is encountered with the requirements of the Quality System. Some examples of events that may lead to a non-conformance are:
- Failure to meet acceptance criteria
- Use of material that has exceeded its use by date
- Stability failures on marketed product
- Unplanned deviations to process or procedural requirements
- Incorrect labelling of samples

The non-conformance must be documented, investigated, a correction applied and a corrective action put in place. A common problem when non-conformances are being investigated is that they tend to be too narrow in their scope. Individuals responsible for investigations need to consider the potential impact on all products that may make use of a common process or material. Also, the investigation should evaluate the impact on product that is already in distribution or with customers.

Investigations
The ultimate aim of the investigation is to determine the root cause of the non-conformance, so that any corrective action, as previously stated, can prevent recurrence. However, the root cause may not be readily determinable and an extensive investigation spread across various departments and disciplines is required. The breadth and depth of such an investigation plan should reflect the severity of the non-conformance and the frequency of occurrence. The plan is developed by a cross-functional team and should contain details of the areas to be investigated, the method/s of analysis, the evaluation criteria and the due date for completion. The findings of the investigation are subsequently documented in a report, which should also detail proposals for corrective actions.

Corrective Actions
Just like the investigation plan, the type of corrective action arising from a non-conformance should reflect the severity of the non-conformance and the frequency of occurrence. Therefore, a non-conformance arising from the incorrect completion of a record may lead to remedial training and the tracking & trending of this class of non-conformance. However, a non-conformance giving rise to a failure to meet release criteria affecting product performance may lead to the revision of procedures, changes in a process, or both.

The type of corrections that may be applied to the non-conformance will be dependent on its nature, but examples are:
- Reworking material/product to bring it back into compliance
- Fixing a document entry error
- Destruction of material/product
Upon completion of the corrective action/s evidence is submitted to demonstrate that all of the required actions have been put in place and are operational.

**Effectiveness Checks**
As part of developing the corrective action, criteria must be determined against which the success of the corrective action in preventing recurrence can be judged. This is called an effectiveness check and takes place after the elapse of a pre-determined period of time. The objective of these checks is to

- Provide objective evidence of completion
- Determine if the desired result/s has been achieved
- Determine if additional hazards or non-conformances have been introduced as a result of the corrective action

**Preventive Action**
Unlike corrective actions, which are a reactive response to an incident, preventive actions arise through the monitoring and trending of data collected from the quality system. The data is reviewed by senior management, either at dedicated CAPA review meetings or as part of the Management Review process. Management can instigate an investigation or corrective action should an adverse trend be seen before any non-conformance has occurred.

**The Role of Management**
At key stages throughout the CAPA process documentation is required to be reviewed and approved by Senior Management prior to commencement of the intended action. This serves two purposes,

- To provide visibility to management regarding the CAPA process as part of management’s commitment to reviewing the effectiveness of the quality system
- To ensure that the proposed actions are aligned with management expectation

**Conclusion**
CAPA must be regarded as a key element of any company’s quality system and you ignore it at your peril. You only have to visit the FDA website to see the large number of citations regarding CAPA system deficiencies to realise that this is an area receiving increasing regulatory focus.

This article does not go into the detailed workings of a CAPA system since there is no one solution that fits all, but if you would like to discuss further please contact the author at a.tipping@qvsltd.co.uk.
We have all used the acronym ‘CAPA’. We may even have given it the proper name of ‘Corrective and Preventive (not Preventative) Action’. Surely this is the territory of pedants – who cares what it is called as long as we know what it means!

But, do we?
A quick survey of QA Professionals showed that most thought that Corrective and Preventive Action meant sorting it this time and making sure it did not happen again. Then we have the concept of ‘improvement’ which deals with anticipating other areas of risk, but don’t let’s get too worked up about hypothetical risks that have not yet happened.

There is a minor inconvenience with this approach. The International Standardisation Organisation in its ISO 9000 series uses these definitions:

preventive action: action to eliminate the cause of a potential non-conformity or other undesirable potential situation

corrective action: action to eliminate the cause of a detected non-conformity or other undesirable situation

correction: action to eliminate a detected non-conformity (3.6.2)

NOTES: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. There is a distinction between correction (3.6.6) and corrective action.

So, it isn’t really CAPA – it is CCPA!

For example, if I have a headache I take a painkiller to take the pain away. That is correction. I notice that I get the headache when I have been working at my computer for some time and I get my eyes tested.

This reveals that the cause of the headaches is eye-strain and a pair of spectacles prevents the headaches recurring by removing their cause. That is corrective action. While researching the possible link between using computers and headaches I noticed that cases of repetitive strain injury are becoming more common. I don’t have this but I am persuaded that I can prevent this developing by using a wrist rest with my mouse and keyboard. This identification and removal of potential problems before they happen is preventive action.

Old habits die hard. The European Forum for Good Clinical Practice has recently published a revision of its ‘Engage’ guidelines, specifically to take account of developments such as ISO 9000:2000. Unfortunately it does not include correction, corrective action or preventive action in its extensive glossary but it does refer to ‘corrective, preventive or improvement actions.’ (See table below)

Personally, I believe that the ‘traditional’ terminology as used in the Engage Guideline is easy to understand and the publication of the ISO 9000:2000 definitions has brought unnecessary confusion. The increasing trend of looking beyond fixing things to preventing real and potential problems is to be welcomed. Perhaps the real challenge will be to communicate what we mean clearly and un-ambiguously.

Andrew Waddell
TOWER MAINS LIMITED

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<table>
<thead>
<tr>
<th>ISO 9000:2000</th>
<th>&quot;Traditional&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixing a defect</td>
<td>Correction</td>
</tr>
<tr>
<td>Preventing that defect recurring</td>
<td>Corrective Action</td>
</tr>
<tr>
<td>Identifying and preventing defects before they occur</td>
<td>Preventive Action</td>
</tr>
</tbody>
</table>

The Medicines and Health Products Regulatory Agency (MHRA) Inspectorate

Summary
MHRA Inspectors perform inspections in Good Laboratory Practice (GLP), Good Clinical Practice (GCP), Good Manufacturing Practice (GMP), Good Distribution Practice (GDP), and Good Pharmacovigilance Practice (GPvP). This paper details how this apparently diverse range of inspections is organised. The management structure is detailed as well as common processes.

The content of these inspections will also be outlined in a further article to be published in the next issue of Quasar.

Introduction
At a recent MHRA conference it came as a surprise to some that the MHRA Inspectorate and Enforcement (I & E) Division no longer existed. The former I & E Division has become Inspection and Licensing. Within the I & S Division there are four Group Managers each of whom report to the Head of the Division. The Divisional Management structure is given in Table 2 (below).

The names and contact details of the Operations Managers are shown in Table 3 (Overleaf) along with the inspectors in each team. The numbers of non-GMP inspectors out number those in GMP and this trend is set to continue as the GCP and GPvP teams expand to deal with the amount of regulatory work required. Inspectors can be away from the office (inspecting) for prolonged periods. To ensure effective communication normally all management teams meet once a month and all inspectors have monthly one to one meetings with their managers. Operations Managers allocate up to 60% of their time to inspection. Key to the Inspectorate structure is the maintenance and development of common systems and the flexibility to anticipate new requirements.

For those inspectors that are not managers there are three technical career grades these are Accredited Inspector, Senior Inspector and Expert Inspector. Generally the degree of complexity of work undertaken increases as an inspector progresses through the technical grades. Senior and Expert Inspectors provide leadership in technical areas. They are sometimes referred to as lead inspectors. Technical meetings are held at routine intervals by Senior and Expert Inspectors. The frequency of which depends on the GXP area and the scope of the work performed. Senior Inspectors hold the same civil service grade as the Operations Manager. Expert Inspectors have the same civil service grade as the Unit Manager. It is emphasised that Table 3 (Overleaf) is a staff structure diagram only. It does not indicate how inspectors interact across the various good practices.

Table 1 - The GXP Inspectorate
Good Laboratory Practice (GLP)
GLP Inspectors conduct inspections of facilities that carry out non-clinical studies for submission to regulatory authorities to assess the safety of new chemicals to man, animals and the environment. These inspections assess the integrity of the data being submitted. The range of test facilities to be monitored includes those involved in the testing of human and veterinary pharmaceuticals, agrochemicals, food and feed additives and industrial chemicals.

Good Clinical Practice (GCP)
GCP Inspectors assess compliance with the requirements of European guidelines and regulations relating to clinical trials by conducting inspections at the sites of pharmaceutical sponsor companies, contract research organisations, academic research organisations, investigation trial sites, clinical trial labs and non-commercial clinical trial sites.

Good Manufacturing Practice (GMP)
GMP Inspectors conduct inspections of pharmaceutical manufacturers to assess compliance with EC guidance on Good Manufacturing Practice and the relevant details contained in marketing authorisations. They ensure that medicines supplied in the UK meet consistent high standards of quality and of safety and efficacy. Overseas sites named as manufacturing sites for products with UK marketing authorisations are also inspected.

Good Distribution Practice (GDP)
GDP Inspectors conduct inspections of sites used by wholesale dealers for the storage and distribution of medicinal products. Inspections are undertaken against the guidelines contained in European Community’s (EC) Guidelines on Good Distribution Practice for Medicinal Products for Human Use and Rules and Guidance for Pharmaceutical Manufacturers and Distributors.

Good Pharmacovigilance Practice (GPvP)
By conducting inspections at the sites of marketing authorisation holders Pharmacovigilance Inspectors assess compliance with the requirements of European legislation and guidelines in relation to the process of the Company’s obligations in assessing the continuing safety of medicines after placing them on the market.

Summary
MHRA Inspectors perform inspections in Good Laboratory Practice (GLP), Good Clinical Practice (GCP), Good Manufacturing Practice (GMP), Good Distribution Practice (GDP) and Good Pharmacovigilance Practice (GPvP). This paper details how this apparently diverse range of inspections is organised. The management structure is detailed as well as common processes.

Table 2 - I & S Division Management Structure
Depending on experience inspectors can and do work between the various teams. For example, some GLP inspectors inspect GMP contract laboratories; some GCP inspectors undertake GPvP inspections etc. In addition to the teams mentioned certain free-standing teams may also be created as required for specific areas of work e.g. inspection of blood sites (Table 4 - Right). Such free-standing teams will draw staff as necessary from the various Operations Manager teams.

Geographical location

Today all Inspections performed by MHRA inspectors are co-ordinated at a national level from the MHRA headquarters in Market Towers, London. Inspectors (and Enforcement Officers) are based at two “outstations” in addition to London. One outstation is in York and the other in Hitchin. The Hitchin outstation will relocate to Welwyn Garden City in April 2006.

Process vs. Content

It is appropriate at this point to emphasise the distinction between inspection process and inspection content. Process refers to how the work of the GXP Inspectorate is managed and organised. Content refers to the specific (technical) aspects of the area of GXP. The process side of the inspectorate is similar regardless of which good practice an inspector works in and training for this is common to all inspectors. The function of the Inspectorate is to help to protect public safety by making a recommendation to the licensing authority regarding inspection findings. The process by which this is undertaken particularly for adverse inspection findings is the same for all areas of Inspection. Whereas the content i.e. the specifics and technical aspects of what the inspectors in each good practice actually look at on the various sites visited can be very different. As indicated, this and subsequent articles focus primarily on process aspects.

Recruitment

A specific inspector competency profile has been developed and the recruitment and training process strengthened to ensure that all inspectors in post today meet this profile as well as demonstrating the necessary technical competencies. The correct inspector non-technical competency profile is key and this profile is continually under review. It is the strict adherence to this recruitment process and appropriate training for those already in post that has allowed the Inspectorate to develop and adapt to changing demands.

All new inspectors undergo up to six months of induction training before becoming an Accredited Inspector. The scope of the various good practices can be very broad; accordingly training is a continuous process. All Inspectors have a personal development programme and are assigned up to 10 days of formal training each year, which includes an annual five-day GXP residential programme and are assigned up to 10 days of formal training a continuous process. All Inspectors have a personal development e.g. those for the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and EMEA (European Medicines Agency).

Quality System

All parts of the Inspectorate are accredited to ISO 9001 and inspections are undertaken in accordance with management approved documented standard operating procedures. This means that all good practices are subject to regular (annual) in-house audits by the MHRA Quality Standard Officer (GSO) and external audits by ISO inspectors. There is a rolling programme for these external audits such that all parts of the quality system are reviewed once every two years. There is also a peer review audit process of on-site activities performed by Expert Inspectors (or their designees).

Expert inspectors set the programme for these audits (across the whole of GXP) each year such that all inspectors are audited on site at least once every two years. In addition for each inspector a number of inspection reports are also reviewed between audits. Expert Inspectors (and designees) performing these inspector audits are themselves audited by the QSO at least once every two years.

Any adverse findings arising from any of these audits would result in appropriate corrective action, which may include re-training. As an additional quality measure a record is kept of all inspection non-compliances to industry. For larger inspection populations any inspector bias can be detected. These inspection statistics for GMP have been published in the Pharmaceutical Journal (ref. Taylor et al Pharmaceutical Journal, vol 270 25th Jan. 2003).
Interaction with stakeholders

A pro-active role is taken in communication with stakeholders. This includes Pharmaceutical Companies, academic bodies, professional bodies and groups within the UK and other Agencies in the UK and in the rest of the World.

Inspectors participate in regular consultative committee meetings with representative from industry, academia (where appropriate), other government departments and appropriate professional bodies. Consultative committees exist for GMP & GDP, GCP/GPV, Blood Inspections and GLP. Common issues and concerns arising from inspection can be discussed at these meetings as well as regulatory changes. Aspects of a more technical nature and issues such as the top ten non-compliances arising during inspection are presented at regular MHRA Inspectorate Symposia. Tables 5 & 6 respectively give details of the consultative meetings and the symposiums held.

Feedback is also sought from stakeholders. Questionnaires are forwarded on a regular basis to sites inspected, these aim to determine if the inspection improved the quality system at the organisation visited. All responses to these questionnaires are returned to the QSO who reviews them in line with the appropriate parts of the quality system.

The MHRA Inspectorate regularly contributes to inspection meetings around the world. Managers and Senior and Expert Inspectors attend OECD (Organisation for Economic Co-operation and Development) and EC meetings and contribute to the steering committee at PIC/S as well as taking a leading role in PIC/S expert circles, and EMEA and EU Commission working groups.

On a European basis MHRA Inspectors participate in all EMEA ad hoc GMP and GCP Inspectors meetings. A significant contribution to the EU Inspectorate knowledge base is also provided.

Inspector training is offered to other Member States and EU Inspector training courses are offered by MHRA e.g. a Pharmacovigilance Inspection training course was run in November 2005 and a “How to inspect” course was run for EU Inspectors in Edinburgh last year. This is in addition to training given to specific EU Members States through MHRA twinning arrangements e.g. that with Czech Republic.

Conclusion

The structure of the Inspectorate is continually evolving in response to changing demands. This and further articles record the structure and function of the MHRA Inspectorate as it is today. Hopefully a greater understanding of how the Inspectorate is organised to undertake statutory inspections and the process for dealing with the outcome of these inspections will assist industry in its interaction with the MHRA.

The GLP Monitoring Authority (GLPMA) undertakes work on behalf of five receiving authorities. One of these receiving authorities is the MHRA. The GLPMA is located within the MHRA and whilst it functions as part of the GXP Inspectorate, it retains its independence as a separate Monitoring Authority. Separate liaison committee meetings are held with all receiving authorities once per year.

* The GLP Monitoring Authority (GLPMA) undertakes work on behalf of five receiving authorities. As part of the GXP Inspectorate, it retains its independence as a separate Monitoring Authority. Separate liaison committee meetings are held with all receiving authorities once per year.

<table>
<thead>
<tr>
<th>Consultative Committee</th>
<th>Frequency (x/year)</th>
<th>Secretary</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP</td>
<td>1x</td>
<td><a href="mailto:andrew.gray@mhra.gsi.gov.uk">andrew.gray@mhra.gsi.gov.uk</a></td>
</tr>
<tr>
<td>GMP/GDP</td>
<td>2x</td>
<td><a href="mailto:david.olszowka@mhra.gsi.gov.uk">david.olszowka@mhra.gsi.gov.uk</a></td>
</tr>
<tr>
<td>Blood</td>
<td>2x*</td>
<td><a href="mailto:andrew.hopkins2@mhra.gsi.gov.uk">andrew.hopkins2@mhra.gsi.gov.uk</a></td>
</tr>
<tr>
<td>GCP</td>
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<td><a href="mailto:gall.francis@mhra.gsi.gov.uk">gall.francis@mhra.gsi.gov.uk</a></td>
</tr>
<tr>
<td>GPvP</td>
<td>2x</td>
<td><a href="mailto:patricia.moore@mhra.gsi.gov.uk">patricia.moore@mhra.gsi.gov.uk</a></td>
</tr>
</tbody>
</table>

* First meeting January 2006

Statistics for other areas of GXP have been presented at various MHRA Symposia and can be obtained from the conference organisers (conferences@mhra.gsi.gov.uk).

Other organisations also audit the Inspectorate. The FDA (as part of the pending Mutual Recognition Agreement (MRA) with the European Union (EU)) & the National Audit Office have both audited in recent years. Specific good practices are also subject to regular review by external auditors e.g. GLP have been subject to a Mutual Joint Visit and GMP will be reassessed by PIC/S in April this year. In general the findings from such internal and external audits have identified only minor issues.

Table 5 - Consultative Committee Meetings

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryan Wright</td>
</tr>
<tr>
<td>Bryan Wright joined the MCA (now the MHRA) in 1989, having previously worked in community and hospital pharmacy. Having fulfilled numerous senior roles within the Inspectorate Bryan is now Unit Manager with responsibility for Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Good Clinical Practice (GCP), Good Pharmacovigilance Practice (GPvP) and Good Distribution Practice (GDP) as well as being Head of the GLP Monitoring Authority.</td>
</tr>
</tbody>
</table>

Table 6 - Symposiums involving MHRA Inspectors

<table>
<thead>
<tr>
<th>Year</th>
<th>Clinical Trials &amp; NHS</th>
<th>GLP Inspections</th>
<th>How to inspect*</th>
<th>GMP Inspections</th>
<th>Pharmacovigilance Inspections</th>
<th>GDP Inspections</th>
<th>Pharmacovigilance Practice (GPvP)</th>
<th>GCP Inspections</th>
<th>Blood &amp; Safety Regulations (x4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>APIS</td>
<td>GLP Inspections (x2)</td>
<td>Getting the best from MHRA</td>
<td>GMP &amp; Stem cells</td>
<td>How to Inspect*</td>
<td>Pharmacovigilance</td>
<td>GMP Inspections</td>
<td>How to inspect* (x2)*</td>
<td>Pharmacovigilance for Inspectors*</td>
</tr>
<tr>
<td>2004</td>
<td>2005</td>
<td>2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>2006</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>GMP (March)</td>
<td>GCP (May)</td>
<td>GCP (June)</td>
<td>Pharmacovigilance for Inspectors*</td>
<td>Pharmacovigilance</td>
<td></td>
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</tr>
</tbody>
</table>

*Available to Inspectors only
Pesticides registration, monitoring in the environment and responsible use

Pesticides review procedures and current legislation

The term ‘pesticide’ covers a large range of products used to control pests; it covers products which are used to control insects, weeds, moulds and fungi to rodent killers and bird and animal repellents. Pesticides can be used by both professional users, for example in agriculture or pest control services, and amateur users in the home or garden. All pesticides need to be registered before they can be used. In the UK, the advertisement, sale, supply, storage or use of any pesticide is prohibited unless it has been approved by the appropriate regulatory authority and government ministry. The registration processes can vary depending on whether the pesticide is used for plant protection purposes or non-agricultural use. Nevertheless the purpose of the registration procedure is the same, that is, to prove that use of the pesticide does not result in harmful effects to human or animal health or the environment, when used as recommended on the product label.

All of the chemicals used in pesticide products which afford the pesticidal properties or action of the product, are termed the active ingredients. The European Union has established a programme of testing and data review for all pesticidal active ingredients which are currently on the market throughout the EU. This review programme, established under Council Directive 91/414/EEC for plant protection products or under Council Directive 98/8/EC for non-agricultural pesticides aims to harmonise registration processes throughout Europe and to provide a review of older chemicals to modern, stringent, safety standards. Only active ingredients which meet these standards are placed on a positive list (Annex I of the Directive) and product authorisations permitted.

Numbers of active ingredients and costs for review

For agrochemical active ingredients, more than 700 active ingredients were listed for review under Directive 91/414/EC, in a process that started in 1993. For each active ingredient, the manufacturing company had to provide a dossier containing scientific test data on a range of the properties of the material – chemistry, toxicology, ecotoxicology, fate in the environment, residues and efficacy. The costs to industry of supporting each active ingredient in the EU have been estimated by the European Crop Protection Association to be Euro 3.7 million, which has had an impact on the number of actives which have been supported and the diversity of products available to farmers. Indeed it has been estimated that more than 60% of active ingredients may be lost to farmers over the coming few years.

Monitoring of pesticides in food and water

Food

The stringent regulatory procedures allow a prediction, based on scientific knowledge, of how a pesticide will react in the environment and the level of any residues which may remain. Residue levels in crops, water courses and soil are predicted using data from laboratory studies and measured against the predictions in field studies. The levels of pesticide found in the environment are not always related to the amount used, but also depend on the properties of the chemical. For example, for an agricultural pesticide the level of water residues depends on how much is adsorbed to the soil, how quickly the pesticide may degrade and how long it has been between application and first rainfall.

Measures are implemented by governments to monitor pesticide residue levels. For example, controls on the amount of pesticide permitted in food are in place throughout the EU, via legislation defining the maximum residue levels (MRLs) permitted for individual pesticides in each type of crop. MRLs are based on the maximum residue that will occur when a pesticide is used according to its terms of registration approval.

1. See Pesticides Safety Directorate Homepage http://www.pesticides.gov.uk/
4. www.prc-uk.org
During the evaluation procedure for registration, the MRLs are compared with toxicity data developed over many years which allow a safe level of human intake to be established. It is illegal to sell a crop with residues above the MRL and thus a programme to monitor foodstuffs for pesticide levels is conducted every year in the UK by the Pesticides Residues Committee.\(^4\)

**Water**

Much EU legislation has been published over the years which covers water quality, and this has largely been integrated into the Water Framework Directive, 2000/60/EC. The Drinking Water Directive 98/83/EC has prescribed limits for pesticide levels in water intended for human consumption. Within the Directive the Maximum Admissible Concentration (MAC) for any individual pesticide is 0.1 µg/l with a limit for total pesticides of 0.5 µg/l. These limits are not based on scientific data, but rather, are a substitute for zero, that is not present or below the limit of detection of the analytical method.

In the UK, the Environment Agency oversees water quality testing and has established maximum concentration limits for some pesticides in rivers, lakes and coastal and estuary waters. Each of these limits, called Environmental Quality Standards (EQS), is specific to an individual pesticide and is determined from the testing conducted to establish its toxic properties to aquatic life.

**What is done to encourage responsible use**

There are many sources for information for farmers and agronomists to encourage responsible use of agricultural pesticides. The Green Code\(^5\) is published by the UK MAFF and covers such topics as minimisation of pesticide usage, protection of the user and the public, protecting wildlife, keeping records and disposal practices.

The Voluntary Initiative\(^6\) is a 5-year plan, initiated in 2001, by the Crop Protection Association to try to lessen environmental impacts of pesticides through new technologies, best practise and education. The Initiative was implemented in place of a tax on agricultural and horticultural pesticides. One of the main projects of the Initiative is to work closely with farmers and water authorities in pilot catchments to reduce water contamination, notably for pesticides that are most commonly found in monitoring studies, and to extrapolate the lessons learned across the whole country.

The Pesticides Forum\(^7\) was established in 1996 to provide advice on best practice to both the Government and pesticide users. A wide range of interested parties is included in the membership of the Pesticides Forum, from non-governmental organisations, food producers associations, wildlife conservancy groups and pesticide advisory bodies.

**Enforcement of pesticides legislation**

Responsibility for enforcing pesticides legislation in the UK is shared between the Health & Safety Executive (HSE), local authorities, the Department for Environment Food and Rural Affairs (DEFRA, which includes the Pesticides Safety Directorate), the Scottish, Welsh and Northern Ireland administrations, the Environment Agency in England and Wales (EA), and the Scottish Environmental Protection Agency (SEPA).

In general the HSE’s concern lies with pesticides where they are used as part of someone’s job, whereas PSD enforces legislation on products used in agriculture and in the garden. DEFRA/PSD and the Scottish, Welsh and Northern Ireland administrations are responsible for monitoring the effect of agricultural pesticides on wildlife. Local Authorities have the authority for carrying out enforcement action locally where food safety is threatened.

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Liz Macquarrie has been working in the area of European crop protection product registration for more than 10 years. She is currently Regulatory Affairs Manager for the Danish agrochemical company, Cheminova A/S. Prior to this she worked for Covance Laboratories as Head of Agrochemical Regulatory Affairs.
Diary Dates

Professional Development Courses

Good Pharmacovigilance Practice
11th - 13th April 2006
18th - 20th September 2006
Wyboston Lakes, Bedfordshire

Research Quality Assurance for Good Laboratory Practice
12th - 13th April 2006
10th - 11th October 2006

Implementing Good Clinical Laboratory Practice
25th - 26th April 2006
4th - 5th October 2006

Good Laboratory Practice for Study Directors, Principal Investigators, Study Staff and Management
9th - 10th May 2006
27th - 28th June 2006
12th - 13th September 2006
28th - 29th November 2006

Systems Audit
16th - 17th May 2006
Wyboston Lakes, Bedfordshire

Good Laboratory Practice for Facility Management
5th June 2006

Audit Steering Group Audit Training
13th - 14th June 2006

The Auditing Course
6th - 7th June 2006
25th - 27th September 2006

Regulatory Compliance and Computer Systems
12th - 14th June 2006

Promoting and Managing Change in a Regulated Environment
12th - 15th June 2006
Ipswich

Process Mapping as a Management and Auditing Tool
19th - 21st June 2006
4th - 6th December 2006

Monitoring Clinical Laboratories
7th September 2006
Novotel, Heathrow

Observation and Recording for Auditors
11th - 13th September 2006

Audit Analysis and Reporting
13th - 15th September 2006

Good Clinical Practice Auditing – Principles and Practice
25th - 27th September 2006

Good Manufacturing Practice for Investigational Medicinal Products
10th - 11th October 2006

Good Laboratory Practice for the Analyst
17th - 18th October 2006

Facilitating Root Cause Analysis
27th - 29th November 2006

All courses and seminars are at Madingley Hall, Cambridge unless stated. For full details of courses and seminars see the BARQA Training Prospectus or visit the website www.barqa.com

Seminars

Network Infrastructure Qualification
20th April 2006
Novotel, Heathrow

Out of the CRF Closet (there is more to life than SDV)
Joint BARQA/ICR Seminar
11th May 2006
Holiday Inn, Kensington, London

Risk Assessment and Risk Management for GxP Computer Systems
24th May 2006

Image Management in a Regulated Environment
6th June 2006

An Inspector Calls
15th June 2006
Novotel, Heathrow

Statistics in Animal Health
29th June 2006
NUT, Euston, London

GMP/GCP Interface - Current Perspectives
Joint BARQA/CSDG Seminar
4th - 5th July 2006

Audit Survival Kit
September 2006

BARQA CONFERENCE
BARQA 2006 Annual Conference
1st - 3rd November 2006
Royal Bath Hotel, Bournemouth
conferences@barqa.com
Latest from the Committee

The Computing Committee last met in January at Madingley Hall, Cambridge, prior to the Compliance and Computers Professional Development course. We have always found running the committee meetings alongside this course enables regular discussion on the course, ensuring that the course material is up to date, reflecting current computing and regulatory issues.

The committee, in conjunction with the BARQA Office, are facilitating a number of one day seminars. These seminars will tackle some of the problematic issues in computing and compliance; issues which are so often neglected, until that fated inspection. If your works concerns computing then you need to consider attending these seminars:

Network Infrastructure Qualification
Novotel, London Heathrow, 20th April 2006
For a time Network Qualification in GxP environments seemed to be a flash in the pan topic or the latest buzzword. Now it appears to be here to stay. Why Qualify your network?

Risk Assessment and Risk Management for GxP Computer Systems
Madingley Hall, Cambridge, 24 May 2006
This seminar, first held in 2005, was acclaimed by membership; its apt timing providing important information on the FDA’s approach to risk management, Part 11 and computerised systems.

Image Management in a Regulated Environment
Madingley Hall, Cambridge, 6th June 2006
This seminar proved extremely successful last year and will be held again. It will provide important information on how to manage electronic images in a GxP environment.

Details of these seminars together with booking forms can be found in the BARQA Training Prospectus. Alternatively they are available on the BARQA website www.barqa.com

Discuss issues of computing and compliance with us on the BARQA Discussion Forum or via any committee member.

Delegates at the Image Management in a Regulated Environment Seminar in 2005
The Animal Health Committee has met together formally once since the last update in Quasar. We thank Moredun Scientific in Edinburgh for hosting the meeting on 19th January 2006.

At the meeting, the Committee welcomed Karl Butler who joins the Committee from Intervet. We look forward to involving Karl in the committee’s activities; he brings to the Committee considerable expertise in the field of animal health research quality assurance. We look forward to his contribution.

Matters that arose at the meeting included the BARQA/SQA Monitor Best Practice document which is now completed after considerable work by both BARQA AHC and the SQA speciality section on Animal Health. The document is currently with the BARQA office and Board; we eagerly await its publication in the near future.

The annual BARQA meeting at Bournemouth this year with the theme of ‘Regulation, Risk and Reality’, will have a number of Animal Health proposed speakers in the GLP stream on Day 2.

The Animal Health Committee has been busy organising a one day seminar hosted by Professor George Gettinby on the application of Statistics in GLP and GCP studies. The agreed date for this is 29 June and will be held at the NUT in central London. If you plan to attend, then hurry and book as there is a limited number of places left for this seminar. In addition, it is hoped to hold a Monitors seminar & workshop in early October 2006. This will follow the publication of the Monitors paper by BARQA.

The next meetings of the AHC are a Teleconference on 20 April and a face to face meeting at Pfizer, Sandwich: Kent on 1st June.

USA

The Society of Quality Assurance (SQA) will be giving a full day workshop on "GLP & GCP Comparison: Auditing Animal Health Studies", on Monday 24th April at the SQA 22nd Annual Meeting in Phoenix, Arizona. We look forward to being able to report on this event in future editions of Quasar.

CVMP/VICH guidelines

The latest adopted guidelines by the EMEA’s Committee on veterinary medicinal products (CVMP) are from the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH)

- CVMP/VICH/810/04 corr VICH Topic GL39 Step 7 Guideline on Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances (CVMP adopted November 05)
- CVMP/VICH/811/04 corr VICH Topic GL40 Step 7 Guideline on Test Procedures and Acceptance Criteria for New Biotechnological/Biological Veterinary Medicinal Products (CVMP adopted November 05).

Interpretation of VICH GL9 on Veterinary Clinical Studies

In section 6, ‘The study Protocol’, the following section can be found

6.3.20 Supplements to be appended to the protocol.

6.3.20.1 List any study-specific SOPs that apply to the conduct, monitoring and reporting of the study.

I was clear about the interpretation of this section until it was challenged.

Does it mean SOPs that apply to the conduct, monitoring and reporting of the study in question and likely to other studies as well? This would be an extensive list.

or

SOPs that have been written specifically for the conduct, monitoring and reporting of the study but not general SOPs that are applied to all studies in the area of conduct, monitoring and reporting? This would be a limited list.

In section 4 on Sponsor Responsibilities

4.2.9 Inform the investigator of appropriate chemical, pharmaceutical, toxicological, safety, effectiveness and other relevant information as a prerequisite to conducting the study. The sponsor should also inform the investigator of any such pertinent information that becomes available during the study and when required, ensure that the relevant regulatory authority is also notified.

The interpretation of the middle section is one that is the cause of much discussion. ‘The sponsor should also inform the investigator of any such pertinent information that becomes available during the study’. An interpretation is that information becoming available will be provided to the Investigator, which if it had been available at the start of the study would have been in the scope of the first sentence of section 4.2.9. That is, ‘appropriate chemical, pharmaceutical, toxicological, safety, effectiveness and other relevant information as a prerequisite to conducting the study.’ By this interpretation, the quantity of information passed onto the Investigator is limited.

You may have your own interpretation of these sections of VICH GL9 or of other sections that are open to various interpretations. If so, we would like to hear from you.
Avian Influenza
International Federation for Animal Health

Global news headlines are filled with reports about the spread of avian influenza, or “bird flu,” and the possibility it could become a global pandemic in humans. The animal health industry, which researches and produces a range of products to prevent and treat disease in animals, has worked with government authorities, stakeholders and poultry producers and developed vaccines that can help address the spread of this disease in poultry.

Although avian flu has primarily been an animal disease to date, experts fear the virus could mutate into a form that could be spread among humans. While governments around the world are justifiably preparing for the possibility of a human pandemic, it is important to realize that the best protection for human health is the control and eradication of the disease in animals. The threat of avian flu spreading to humans is a clear demonstration of the interrelationship between animal health and human health, and the important role animal health and animal health products can play in protecting public health.

Background
Avian influenza (AI) is a respiratory disease of birds caused by a virus. There are several different types. Outbreaks of low pathogenic avian influenza (LPAI) are common around the world. The high pathogenic avian influenza (HPAI) is more serious due to its higher mortality rate in affected birds. The type currently spreading in Asia and in wild birds in Europe is referred to as H5N1 HP AI. The ‘H5N1’ designation comes from the arrangement of two proteins on the surface of the virus.

Avian flu is transmitted from bird to bird within a flock or poultry house mainly by inhalation of the airborne virus and by contact with the virus shed in the faeces from infected birds. It can be transmitted from poultry house to poultry house by contact with contaminated equipment or the movement of people who can carry contamination on their clothing and footwear. While the most common hosts for the virus are wild waterfowl species, it also has been reported in many common species of poultry, including chickens, ducks, turkeys, geese, pheasants and quail, as well as in a variety of other birds like parrots, cockatoos, and parakeets. Some species are more resistant to infection or can be asymptomatic transmitters of the disease.

Animal Health Products to Help Control AI
A number of animal health companies produce vaccines that are effective in preventing clinical disease in birds. These vaccines help control the spread of AI by increasing the resistance of the vaccinated bird and by reducing shedding of the virus by infected birds.

AI vaccines are currently being used in South America, the Middle East, Asia and in one EU member state (Italy).

Vaccine use is generally controlled by government policy. Internationally, the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) are the two main organizations responsible for monitoring and controlling animal diseases internationally.


Animal health companies also contribute to the control efforts of avian flu with their wealth of knowledge in the field, products to control vector diseases vectors and, not least, by strictly following sanitation measures when visiting farms.

The Manual of Diagnostic Tests and Vaccines for Terrestrial Animals of the OIE describes the presently available vaccines types and prescribes the standards for these vaccines. Information on the standards for AI vaccines can be found at http://www.oie.int/esp/normes/nnmanual/AI_0003_7.htm.

Vaccines: A Tool in the Fight Against HPAI
The Animal Health industry is actively involved in working with regulatory authorities, stakeholders and poultry producers in efforts to eradicate Al. It is recognized, however, that vaccination alone is not sufficient to prevent the spread of this disease. The AI vaccine, like human flu vaccines, does not prevent the virus from infecting the vaccinated individual. However, it does protect the bird against clinical sickness and death associated with the disease and helps reduce the chance of new outbreaks by reducing the shedding of the virus from infected birds. A concern associated with vaccination is that vaccinated birds may still become infected. Such birds may not have clinical signs and thus disease might be missed in a flock, possibly becoming endemic. Modern vaccines that reduce viral shedding and spreading of virus in vaccinated birds reduce these risks. The level of effectiveness of the vaccine will also depend upon the virulence and pathogenicity of the particular virus.

An effective AI control/eradication programme rests on three important legs:
1) Preventing exposure to the virus in poultry by means of biosecurity controls, such as a set of procedures designed to protect poultry populations from exposure to the virus. In countries with large commercial poultry operations, the birds are typically raised in enclosed buildings designed to provide protection from various types of disease carriers, but once the infection has taken hold in a flock it can spread quickly throughout that building. The spread of the disease has been facilitated in Southeast Asia by the fact that chickens, ducks and other poultry often run at large in the villages in close proximity to each other and to people, whose clothing or footwear may inadvertently transport the virus from one bird to another.
2) Rapid culling of infected birds. Since most poultry flocks are free from Al, the generally accepted response when an outbreak has occurred is to stamp out the virus by eradicating the affected flocks.
3) Vaccination, which can be effectively used as part of an eradication program to stop the spread of the virus. Vaccination reduces shedding of the virus by the bird, both in terms of the period of time of shedding and the concentration of the virus shed.

Vaccination, as one component of an effective control program, has been shown to be successful in helping to eradicate the virus in several countries.

The proper timing and combination of these three tools are decided under the direction of local and national authorities. Globally and on a country-by-country basis, the animal health industry is working with and will lend all possible assistance to the authorities in the battle against this serious disease.

November 2005

Other resources:
World Organization for Animal Health (OIE) at www.oie.int/eng/eng_index.htm
United States Department of Agriculture at www.aphis.usda.gov/2005/10/0459.html
United States Government information at www.pandemicflu.gov

Article courtesy of International Federation for Animal Health Europe
We have had two meetings since the copy date for the January edition of QUASAR. Our December meeting was held at the BARQA office in Ipswich. We also held a meeting in January at Bayer, Newbury.

At both meetings we covered a full agenda. One of the items relates to the BARQA website and working out how to revamp the E&TC part. We will endeavour to keep this up to date. If there is something you would like to see in the E&TC pages of the web, let us know.

The PDCs have been running well. BARQA now has a strong following in Finland after a number of courses have been run there. If there are courses or seminars that you feel you would like to participate in - most of these are not in Finland but at Madingley Hall, Cambridge - these are in the BARQA professional development prospectus recently sent out to all members.

The students on the Masters course run by Anglia Ruskin University have been steadily working away. The majority of the students from the first cohort in 2003 of the Masters will be completing their dissertations by July with graduation later this year. The 2004 students are currently submitting their dissertation plans for their final year.

Following on from the successful pilot (the feedback was really good), we have agreed to create a business plan for the Auditors’ Passport scheme. The scheme is going to require much effort by the BARQA Office with input from the various committees but we firmly believe it will be worthwhile for the membership. Following a presentation on CPD for advanced auditors to the E&TC in January by Sue Gledhill we are looking at how to support the experienced auditor through the passport scheme.

Lynne Spencer has been busy identifying speakers for the E&TC slot in the Annual Meeting to be held in Bournemouth this coming November. We have reviewed feedback over the last few years and plan to have something for everyone.

At our January meeting, Gail Wood, long time stalwart of the committee, tendered her resignation. Gail was involved with the management of the Masters at ARU, particularly by acting as the committee representative for the 2004 students. Gail also was responsible for our contributions to QUASAR, and has been Annual Meeting representative/Session Chair. We wish her well in her extended role at Covance.

I am not saying that Gail did the work of four people (or maybe I am!) but we have now selected four new members of the committee from the long list of applicants wishing to join. For those of you who didn’t make it this time, we still have you in our records. The new members are: Lee Cooke, Peter Knapp, Dave Butler and Steve Nicholas. Between them they bring a broad range of experience and interests in GxPs, Quality Systems, training, Continuing Professional Development (CPD) and distance learning. Our first meeting together will have taken place in March.

John Varley, Chair
Workshops – easy option, or value added?

Many training courses, both in-house and commercial, will include one or more workshop sessions. The scenario is commonplace – delegates are split into groups, given a small task to perform or topic to discuss, herded off into another room and left alone for half-an-hour...

In these open-minded days of 360° appraisals, seeking feedback is commonplace – and workshop performance is no exception here. Interestingly, feedback on workshops shows a fairly predictable pattern: within every group, there’ll be some who loved it, some who hated it, some who lost the plot completely and some who just wanted to keep going for hours. Oh - and always, always, some who were ‘rushed for time.’ Guaranteed.

So what is the purpose of a workshop, even a series of workshops? Well, the first point is that there has to be a point… the workshop should have a real purpose and not appear in the schedule just to pad out time or give presenters a break from talking! Workshops should be properly designed to deliver structured learning for the delegates, or to enable focussed discussion and exploration of a particular subject. It never ceases to amaze me how little material is actually required to feed a workshop group for twenty minutes, half-an-hour, or longer. Equally though, complex discussion topics presented as curt one-liners can stifle exploration, so that delegates never get below the surface of a topic – and that’s really no better than listening to someone reading a PowerPoint slide out loud.

Workshop design is not a five-minute job, not as simple as dashing off a quick sheet with a couple of scenarios and inviting answers to potential issues which might crop up in an imaginary world. A well-designed workshop has elements which are carefully designed to elicit specific – and specified – learning outcomes. Workshop composers will often already have a strong opinion on the intended outcomes, hold a fundamental understanding of the discussion topic or simply know all the answers. Rather than start with the question or discussion topic, it can often be beneficial to write the learning outcomes first, and work backwards. Another useful tip is to pilot the workshop on some unsuspecting colleagues and get some honest feedback… then adjust either the material – or the time allocated – to provide a better fit before going live with real delegates. But it isn’t just about getting the timing right – vague material can allow delegates to get way off topic, become confused or completely fail to understand the basic principles of the topic. Conversely, over complicated material (especially doctored ‘real-life’ stuff) nearly always wastes time by encouraging unpredicted explorations and sometimes even throwing up previously unseen issues in the real work from which the material was lifted!

Getting the material and the timing right is only half the battle, however. Every delegate is different – we all learn in different ways, at different speeds and sometimes in different languages (and some don’t want to learn at all!) Here’s where the facilitator comes in, and come in they must if the workshop is to be worthwhile and add value to the training event.

In fact, a good facilitator is essential if all the delegates are to gain the right messages and experience from their workshop. Effective facilitation is actually quite a challenging task, a real art. Making sure everyone is equally involved, that discussion remains focussed on the topic in hand and that the group delivers the required output in the desired timescale can be incredibly hard work for the facilitator – especially where delegates have wide-ranging views or backgrounds. Getting to the end of a break-out with a clear consensus, vibrant flip-charts or a couple of slick overhead transparencies can often be a real relief… but even then the facilitator’s work is not done. Plenary feedback sessions at the end of a workshop where more than one group has discussed the same issues can be the real turning point for those delegates who may not have gained the clearest of pictures. Drawing out and reinforcing key messages, unravelling misconceptions – even exploring sub-issues – when all the delegates are reassembled is where the facilitator can really add value to the overall learning experience. Get it wrong here and all the preparation, piloting and people skills under the sun can be completely wasted; the last thing delegates want is to spend half an hour getting their heads around something only to have their understanding shattered in the wrap-up.

Workshops remain one of the best mechanisms around for learning – especially so when they are well designed and expertly facilitated. Next time you finish a training course and realise the only bits you recall are the workshop outcomes, just remember it won’t have happened that way by chance.

Roger Chapman
QA DIRECTOR, HUNTINGDON LIFE SCIENCES
BARQA RQA for GLP Course Tutor
Good Clinical Practice Committee News

Committee Activity Update

Hot Topics
Preparation for the next BARQA AGM in 2006 is well underway. The location will be Bournemouth 1st - 3rd November, 2006. Please book these dates in your diary! Already, there is a lot of activity and the Committee members are drafting a programme and identifying speakers for the conference.

Committee Meetings
The GCP Committee has held one teleconference and one meeting, courtesy of Bruce Seymour-Taylor (J & J, Bucks) since the last update on activities.

Meetings
Two ONE day meetings are being planned by the GCP Committee and include:
- An Inspector Calls – 15 June 06 – location at Heathrow, London. This meeting is about GCP and PV inspections as identified by members as a key area of interest.
- Out of the Closet – joint ICR/BARQA – 11 May 06, location at Kensington, London. There will be both presentations and workshops, plenary and panel discussions on several topics i.e. local labs, e-records and inspectors findings.
- Possible - So You Want to be an Auditor/ Audit Survival Kit – Sept 06; details to follow
- GMP/GCP Interface-current perspectives – 4-5 July 06; details to follow
Watch out for updates and flyers to book early as a great deal of interest has been noted!!

Web Site
The GCP web pages continue to be updated by Martha and it is worth having a regular review of the site. The EU CT Directive document has recently been updated on the web. The website is being updated shortly with emphasis on customer focus and ease of access to information.

GPvP Working Group
This group, set up and led by Alison Brown of the GCP Committee, will become a full BARQA committee this year. There have been several applications to join the group which will, in future, be led by Allison Jack as the group moves forward in this extremely important and diverse area. Well done to Alison Brown for this achievement and initiation from the GCP Committee.

Members’ Questions
Questions are submitted mainly to the Committee or via the BARQA office staff. The questions are reviewed by the GCP Committee and responses are published in Quasar. Please note that the views expressed are a collation of GCP Committee members’ personal opinions based on the information provided.

Members’ Feedback
The GCP Committee would like to hear from any members on ideas or items you wish us to progress or actively be involved in. Perhaps you would like to write an article for Quasar. If so, please contact one of the GCP Committee members. However brief it might be, there is always an interest in GCP/QA related articles.

Sally-Ann Black
SECRETARY
GCP COMMITTEE
QUERY - Regarding changing the expiry date of Investigational Medicinal Product (IMP) at study sites

Investigational Medicinal Product (IMP) is currently at several UK sites (trial is active; IMP originates in UK) and has 30 days until it expires. The Clinical Project Manager wishes to visit the sites and amend the expiry dates on the IMP labels, by hand. EU GMP Annex 13 (part 47) states that any re-labelling should be carried out by the manufacturer or another authorised manufacturer and certified by the QP. Can the label be amended by e.g. the Project Manager providing there are instructions for this with authorisation to do this, along with relevant documentation to support the extension to the expiry date provided by the Sponsor?

GCP COMMITTEE RESPONSE (prepared by Alison Brown)

It is our understanding in the UK that re-labelling of expiry date can be performed by a Sponsor representative at the site (Annex 13 mentions the clinical trial monitor) provided there is a specific and standard documented procedure, the person doing the re-labelling has been appropriately trained and that the re-labelling takes place according to GMP principles (e.g. second person checking the re-labelling, reconciliation of labels etc). The new (printed) label should have the new use-by date and repeat the batch number, and it can be super-imposed on the old use-by date but must not cover the original batch number (Annex 13, clause 33). The additional labelling should be documented in both the trial documentation and the batch records. There must be data (documented on file) providing valid support of the expiry date extension. There should also be appropriate documentary evidence on file reflecting the GMP training of the person undertaking the re-labelling.

It is also recommended that in view of the EU CTD, the QP should have oversight and agree with issues to do with labelling and care of IMP.

In Germany, there have been two relevant changes in the 14th Amendment of the AMG (German Drug Law) which became effective 9th September 2005:

• § 9: only the Sponsor (or CRO) needs to be mentioned on the label and not the producer of IMP (Pharmazeutischer Unternehmer)
• § 14 (4) 2: changes of expiry date of IMP at the site can be done by a person authorized by the Sponsor - there is no specific person or job group specified, hence EU GMP Annex 13 applies.

It is, therefore, possible to send a trained CRA to perform the re-labelling with a specific written procedure and a second person verifying the correctness of the re-labelling.

QUERY - Regarding the Declaration of Helsinki

Do companies refer to compliance with the Declaration of Helsinki (DoH) in their protocol and if so, with which version?

GCP COMMITTEE RESPONSE

Consultants questioned stated that they had not come across any protocols that failed to reference DoH. There were a variety of version dates used.

CROs contacted said that they quoted compliance with the version requested by the sponsor and that this varied between 1996 and 2000.

Contacted Sponsors provided a variety of answers as to what their protocols ‘complied with’ or were ‘in accordance with’ the DoH:

• Two companies used the most recent version
• One company quoted 2000 version
• One quoted 1996 version
• Two wrote that their protocols claimed to be ‘consistent with the principles that originated in the DoH’ – but did not quote a specific date
• One company had no mention of DoH at all
Good Laboratory Practice
Committee News

The Committee has met on two occasions since its last report in Quasar; at Battelle AgriFood on 13th October 2005, and HLS on 26th January 2006. Thanks on behalf of the Committee to Aggi Joannou and Vanessa Grant for making the necessary arrangements.

There have been a couple of changes to the Committee membership during this time. First, it is with a note of sadness that we report the resignation of Imogene Heathcote (Syngenta) from the Committee. Imi has contributed much to the Committee and will be missed for her friendly personality, experience and the dedication. Thanks Imi.

Christina Olsen-Sundelin (AstraZeneca) proved to be a capable deputy for Sue Gledhill during her three-month secondment to Sweden. Sue’s assignment is now completed and she has returned to the Committee. Thanks Christina, and welcome back Sue. We are delighted that Vicky Massie has recently joined the committee. She was not included in the original merger of the Field Studies and GLP Committees because she was on maternity leave at the time. So welcome to the fold, Vicky!

Society of Toxicologic Pathology Position Paper: Pathology Image Data

The US Society of Toxicologic Pathology has produced a draft position paper which defines the use of pathology images, both film and digital, in non-clinical studies. The Committee took the opportunity to review this document and has forwarded our comments to the BARQA Computing Committee (which is also looking at this draft position paper), and which in turn will provide all BARQA comments to the STP for its consideration.

Practical Guide on the Role of GLP QA

This guidance document, being prepared by a sub-group of the GLP Committee, is in its final draft. Various parties have been consulted and their comments considered. The final steps for the sub-group are to work with the Office to determine where the document will be published and how it will be distributed to members.

AGIT: Guidelines for the Acquisition and Processing of Electronic Raw Data in a GLP Environment

These guidelines were prepared by the Working Group on Information Technology (Arbeitsgruppe Informationstechnologie, AGIT) and published on 1st December 2005. The AGIT group consists of representatives from Swiss industry and the Swiss GLP monitoring authorities. The aim of this document is to provide guidance on the acquisition and processing of electronic raw data in a GLP environment. This document is available via the GLP area of the BARQA website.

Management of Multi-site Studies Workshop

By the time you are reading this, the above SOLD OUT GLP Committee workshop will have been completed, and 32 delegates will be equipped with practical solutions to the challenges of multi-site studies. Interest in this workshop was so high that a waiting list has been established and every effort will be made to repeat this event soon. Please contact the Office to register your interest.

Archiving Q&A

Question: The UK and OECD guidelines do not appear to give actual times for archiving GLP documents. How long would it be accepted by the regulatory authorities to archive GLP and research documents for a study which has been prematurely discontinued?

Answer: The UK GLPMA is concerned with monitoring regulatory studies and therefore will have no interest in the archiving of research documents. In the case of GLP studies, if the work was discontinued, presumably the study would not be included in a regulatory submission (i.e. to support non-clinical safety) and therefore the regulator would have no opinion on the matter.

The decision on how long to archive the research documents or the discontinued non-submitted study would lie with the sponsor/company concerned. There may be good business reasons to retain the documents for a period agreed by Management (e.g. in relation to intellectual property). This could be in accordance with a documented data retention policy. For the discontinued GLP study, the study should be formally closed and a summary report produced; it would then be prudent to retain all study records (initially at the testing facility) at least until the next GLPMA inspection to allow demonstration of proper closure if requested. Some companies would retain the records for a similar period to submitted GLP studies since there is a chance that development of the compound could be continued some years later.
Although the majority of BARQA members are some sort of quality monitor or manager, we know that there are several GLP Study Directors out there. The BARQA Board is concerned that the Association provides a service to all its members, and that as many members as possible contribute to the Association’s activities. In this respect, Study Director members may not have been well served up to now, but we want all that to change.

The Association can provide a forum for those acting as Study Directors to share experience, and provide mutual support and advice, in much the same way as it does for QA personnel. The level of interest will determine the administrative arrangements. But it is well within the imagination to foresee a common-interest Discussion Group, Working Party, Subgroup associated with the GLP Committee or, even a specialist BARQA Committee.

Are you a Study Director (or Principal Investigator) interested in furthering your involvement with BARQA? In particular, would you be willing to be a co-ordinator (SDs should be good at that) to help get such a group started?

Yes? Or even maybe: email me, Rodney Pateman rpateman@safepharm.co.uk NOW before the treadmill of daily work takes over. We’ll help you to use the facilities and experience of the Association to help you and your peers.
Good Manufacturing Practice
Committee News

Latest news ...

As those of you who regularly read this section will be aware, the GMP committee has been on a bit of a recruitment drive – both to replace retiring members and to keep the committee “fresh”. As a result of this tour applicants have been asked to join the committee. At the same meeting Anthonia Chalmers resigned from the committee to take up a position on the new Pharmacovigilance committee. The committee would like to thank Anthonia for her excellent work in support of the committee and wish her all the very best in the new role.

While we are now at full strength as a committee, we would still encourage anyone who would like to support the GMP constituency within BARQA to contact the committee with any relevant articles/issues they might have, especially now as editions of Quasar are to be themed.

Over the last few weeks the committee has become aware of a number of regulatory publications that may be of interest to members.

These are:

FDA Draft guidance: “INDs – Approaches to complying with cGMP during phase I”
PIC/S guides:
PE009-3 Guide to Good Manufacturing Practice for Biotechnology Manufactures.
PI 021-1: Aide-Memoir on GMP Particularities in the Manufacture of Medicinal Products to be used in Clinical Trials on Human Subjects;
PI 023-1: Aide-Memoir on the Inspection of Pharmaceutical Quality Control Laboratories;
PI 024-1: Aide-Memoirs on the Inspection of Biotechnology Manufactures.

While the documents can be accessed via the appropriate web site (www.fda.gov or www.Picscheme.org accordingly), it is hoped that links to the documents will appear soon on the BARQA web site. The committee has also become aware of a number of documents from other industry bodies that may be of interest to GMP committee members. EFPIA (the European Federation of Pharmaceutical Industries and Associations) has issued a Position Paper “EFPIA Position Paper on the Role of the Qualified Person within the European Union (EU) for discussion. This can be obtained from the EFPIA web site (www.efpia.org). Also, a new guide discussing GMP for Pharmaceutical Excipients has been launched by IPEC (International Excipients and Pharmaceuticals council) and PQG (Pharmaceutical Quality Group). This can be obtained via the PQG web site (www.pqg.org).

GMP Annex 1: Proposed amendment


The proposed changes address four issues: environmental classification, media fill acceptance criteria, pre-sterilisation bioburden testing and the handling of partially stoppered lyophilisation vials.

Environmental classification.
The nonviable particle count limits, as given in the table in clause 4 of the annex, are not themselves changed. The amendment is intended to clarify the text around this table, and mostly succeeds, by introducing 5 new clauses. However, a most confusing footnote has been proposed for addition to the table in clause 3 of the Annex stating that, for grade A and B areas in the ‘at rest’ state, and for grade A ‘in operation’:
‘The maximum permitted number of particles at <5 μm is established at 1/m² but for reasons related to false counts associated with electronic noise, stray light, etc., a limit of 20/m² could be considered.’ It is not clear, at least to me, exactly what this means. It is perhaps unfortunate that the authors did not take the plunge and go straight to the limit of 29/m² found in ISO 14644-1, although the proposed new clause 6 does emphasise the value of the 5.0 μ particle count.

Additional proposed changes include some guidance on the procedures for classification (as opposed to routine monitoring), including the recommendation that for classification purposes a short length of tubing connected to the particle counter should be used, to reduce precipitation of particles. Clearly this does not mean that for routine monitoring a long collection tube should be used, thus artificially reducing particle counts.

There is a slight change in the requirement for the frequency of particulate monitoring of grade A areas proposed in the new clause 5, in that monitoring should be either continuous or frequent, and the frequency should be such that all interventions and transient events are captured. There could have been a statement here regarding the justification of the monitoring frequency (where monitoring is not continuous) as part of the validation programme.

Furthermore guidance is given on the selection of sampling locations (the use of a risk analysis approach is recommended).

Media fill acceptance criteria

The acceptance criteria for aseptic process media simulation tests are proposed to be harmonised with those given by FDA in their guidance on handling of partially stoppered lyophilisation vials.

Questions for the MHRA inspectorate

As in previous years, MHRA have agreed to take part in a meeting with the GMP committee in September 2006. The purpose of the meeting is to discuss member’s GMP inspection-related issues with MHRA. Although the meeting will not take place until later in the year please send any questions you want to put to the inspectorate to the committee secretary for consideration.

As always if you have any comments or queries on the issues raised or other GMP – related issues please contact the chairman (edy@newland-gxp.co.uk), secretary (derek.murphy@cambridgeantibody.com) or any other member of the committee.
document ‘Sterile Drug Products produced by Aseptic Processing,’ September 2004. Whilst this is very sensible, the end result is to replace a simple statement ‘The target should be zero growth, but a contamination rate of less than 0.1% with 95% confidence limit is acceptable’ with recommendations, again with the preamble that ‘The target should be zero growth.’ The recommendations gives acceptance criteria for batches up to 5000 units, from 5000 to 10,000, and for more than 10,000 units. As in the FDA guidance, the numerical limits for the last two groups are the same, and, again as in the FDA guidance, ‘1 contaminated unit in a fill of 5000 to 10,000 should result in an investigation, including consideration of a repeat media fill,’ whilst when filling more than 10,000 units ‘1 contaminated unit in a fill of 5000 to 10,000 should result in an investigation,’ with no mention of consideration of a repeat fill, reflecting the lower statistical significance of one contaminated unit in a larger batch.

Pre-sterilisation bioburden

Whilst it is common practice to measure bioburden on each batch before sterilisation, it has not previously been explicitly required by annex 1. This is now rectified, with the exception that the bioburden need only be determined at ‘suitable scheduled intervals’ when an overkill cycle is used. However, when parametric release is used, bioburden determination should be in an in-process control test on every batch.

Partially stoppered lyophilisation vials

The need to handle lyophilisation vials under grade A conditions up to the point when the metal seal is applied is now explicitly stated in the proposed new clause 93. The proposed text accepts that this may not be possible at the capping station, due to particulates introduced. However, it is implicit that this station should achieve grade A conditions when at rest.

Conclusions

The proposed changes are generally sound sense, although they do present both requirements and guidance on how those requirements might be met. There are a few areas that are not clear, e.g. the consideration of a limit of 20 particles >5μm per metre³ and one or two ‘recommendations,’ which will result in different interpretations by different companies, and possibly by different inspectors, but it is to be hoped that these will be ironed out as a result of the consultation exercise.

Questions to the committee:

Q 1 What is your typical review period for SOPs? Ours is 3 years but in an ongoing mock inspection in the US a consultant is indicating that 1-2 years is the industry norm.

A 1.1 In my experience of numerous, mostly small, customers, two years is the most common. Some are annual, but then the proportion of SOPs passed that the review due date is almost always excessive. However, some have three years, and I know two in Germany who have 4 and 5 years as their review period. When I raise this, the response has been ‘our inspector has not raised this as a problem. But no-one I have visited in the UK is longer than 3, mostly 2.

A 1.2 Our normal review period is three years and has satisfied UKUS inspections. There had been requests from MPA for two years but accepted three based on history of examples, some did not need to change more frequently e.g. operation of a balance, and others changed when there was a need. Isn’t it more important that SOPs are in life, with 1-2 years I would suspect that it would be likely for more to be out of life?

A 1.3 We seem to be out of line with ‘industry norm’ of 2 years, but I would still question the need to reduce to 2 years from our current maximum of 3 years. In preparation for an inspection it is worth doing a quick analysis of actual average time to update, and if your processes change as often as ours I would expect this to be around 2 years anyway. Basically what is the added gain if you review an SOP after 2 years just to confirm it is still ok? What really matters is that you are capturing changes that affect the SOP at the time - and I would argue that having a shorter maximum review period is actually encouraging you to be sloppy about updates in between. On inspection of our main US site by the Swedish Authority the 3 year review period was questioned, but we did not agree to reduce this and the site was approved.

A 1.4 Similarly we have been pushed for less than our current review period of 3 years - but so far have resisted. Part of the justification is that it is a MAXIMUM of 3 years - given that things change, our average is closer to 2 years anyway.

Q 2 The UK Guidance on Wholesale Dealing (Orange Guide) requires the appointment of a ‘Responsible Person’ whose duty is to protect users of distributed product from the effects of poor distribution practices. What exactly does this involve e.g., someone to be named as such to the MHRA and if so, in what format- or as a name in our contracts with distributors etc? We have a UK marketing dept. I read in the Orange Guide foreword that wholesalers are required to appoint a RP who has the knowledge and responsibility to ensure that correct procedures are followed during distribution. We don’t do manufacturing in the UK but have providers/distributors.

A 2.1 My understanding is that the RP is named on the Wholesale Dealer’s licence, and therefore on the application for such a licence.

The duties of the RP are spelled out in the UK Guidance on Wholesale Dealing, as stated in the question. If I understand the situation, however, the question concerns the company’s UK marketing department. Unless they have an established warehouse as part of their own company, I don’t see why they would need a WDL, and so they wouldn’t need, and couldn’t have, an RP. The company’s responsibilities are only to verify that their UK (and other) distributors have the appropriate licences, and comply with GDP and the terms of their licences. This would be part of their selection/ audit procedures.

Q 3 A question, Microdosing studies are those where subjects are given a small fraction of the expected pharmacological dose of a drug, to look at things such as ADME. The dose is usually about 0.1% of the expected effective dose. There is a CHMP document on the preclinical requirements for such studies (CPMP/SWP2599/02 rev 1). The question: As far as I can see, despite the small dose these are still clinical trials under 2001/20/EC, and the materials still need to be made in accordance with GDP and are subject to QP certification. Is this true? Are any of you running or aware of such microdosing studies where the materials are made to a ‘looser’ standard of GMP?

A 3.1 I can’t answer from a position of experience but I will say that the Scope of 2001/20 and the definition of a clinical trial I would say there was very little room for manoeuvre.

A 3.2 A trial is a trial is a trial! And the Position Paper you refer to does have ‘...to support clinical trials...’ in its title. I don’t think there is any requirement set-up in basic GMP principles but one might be able to find some justification for not applying them so stringent.

Q 4 We are currently setting up a Phase I trial at a Phase I unit associated with a hospital. They are using the hospital pharmacy to prepare labelled infusion bags of placebo and active (from open labelled vials, so they are doing the blinding). I think that this is a manufacturing operation and, especially as supply is to a separate legal entity, should be performed as a manufacturing operation. However, the unit claims that as it is on the same site as the hospital and is using the hospital pharmacy therefore they do not need a manufacturer’s licence. Who do you think is correct?

A 4.1 MHRA opinion is that labelling is an act of assembly and therefore must be performed under an MA (IMP).
The GPvP course certainly started as it meant to go on with a challenging quiz straight after the initial greetings. We were all required to test our knowledge of the abbreviations commonly used within pharmacovigilance (PV). Although many of the delegates had upwards of 20 years experience in the industry, there were quite a few questions that stumped us. This was an excellent start to demonstrate that we had quite a lot to learn and had better pay attention.

Pamela and John Nickols gave the opening presentations to set the scene, covering at a high level (always a good start in a training course) what pharmacovigilance is, and explaining the regulatory framework. At this point, all delegates should have reached a similar level of knowledge but we also started to realize the immense scope of the subject, and were feeling the first symptoms of a mild panic attack. Fortunately, a coffee break came to the rescue and provided us with the necessary caffeine stimulation to start on the first workshop, which was facilitated by Andrew Waddell, on the role and responsibilities of the Marketing Authorisation Holder. This challenged us to really come to grips with the legislation and resulted in a fairly lively discussion.

Following the workshop were two excellent presentations from a Qualified Person (Pharmacovigilance) or QPPV, John Pincott. These presentations brought us up to date with new legislation coming into effect and the huge responsibilities assigned to the QPPV. Although the QPPVs can delegate many of their activities, they are fully responsible for ensuring that all PV systems and processes are implemented effectively to ensure that the MAH can fulfil its regulatory commitments. John covered both the pre- and post-licensing areas of PV and provided a very valuable insight into the issues facing the QPPV on a daily basis. John’s final words of advice were “Communicate, Communicate, Communicate – it’s good to talk!”

The afternoon session of the first day was focused on defining reportable events (Pamela Nickols) and processing them (Peter Schultz, QPPV). Needless to say, this involved several flow diagrams to clarify what can
sometimes be a fairly complex process. In order to ensure that we remained fully alert throughout, a second workshop was scheduled to test how much we had absorbed!
This workshop looked at assessing and processing events and required us to design a suitable event tracking form based on a specific scenario. This was a very good exercise to try to make a complex process as simple as possible and in a logical order, without omitting anything. Following this workshop was a well-earned course dinner in the splendor of Madingley’s dining hall. As usual, the food was excellent and the wine flowed freely!

The second day of the course focused on many of the practical issues of managing an effective PV system including continuous surveillance and the new requirements of ICH E2E (Pharmacovigilance Planning). A clear, but comprehensive, presentation was provided by Pamela, including a valuable section on risk analysis and management.

With the requirement for electronic reporting coming into effect, Peter Schulz presented the ‘new language of ePharmacovigilance – E2B M2’. Peter described how e-reporting should work, and also presented the reality that only 40 companies were submitting electronic reports. The remaining several hundred companies were not! Workshop 3 required us to complete a generic adverse event activity log (one which Peter had designed earlier) for three different case reports. This provided an excellent insight into the practical application of an event tracking tool and how critical it is to enter information accurately.

The final areas covered were the Pharmacovigilance Quality System (Andrew Waddell) and Regulatory Inspection (Pamela Nickols). Andrew’s talk focused on procedures, quality control, chain of custody, training, audit and common problems. It provided a comprehensive oversight into what should be expected from a PV quality system. Pamela then provided an overview of the PV inspection process and findings. The last workshop was on the PV Quality System and we had to imagine that we were the European QA Manager of a major global company, presenting our proposal for a global PV systems audit to the company Board. The Board was made up of John, Pamela and Andrew (and a very challenging bunch they were too)! A representative from each group had to present the group’s findings and answer the Board’s questions on why so much resource and money would be required! It was great fun and resulted in some interesting debates.

Overall, the two-day course was well constructed, covering all of the key areas in PV at a level that most of us could understand. The course was very well presented by speakers with the appropriate level of expertise. Most of all, it was very good fun!

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The main focus of the meeting was to define terms and references for the Committee and its future focus. Helen Politis-Norton (Pfizer Consumer Health) has agreed to be the secretary for the Committee. Nazrul Khan (Eisai) will take responsibility for updating the GPvP web pages when the new BARQA website is launched.

The Committee spent some time talking about the Good Pharmacovigilance Practice course with the new course tutor, Ron Ward. In addition to this course we will be looking at others ways to enable members to get the training they require to audit in the area of Pharmacovigilance, so watch this space.

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Report on the 29th Meeting of the Scottish & Northern Regional Forum.

The group had its meeting at Pentlands Management Systems Ltd. (PMS), Midlothian Innovation Park, on the 21st September with the theme of, ‘QC, Assisting QA Function?’ We have tried on this occasion, perhaps ambitiously, to cover the different aspects of QC within GLP, GMP and GCP. Our regular slot of ‘new recruits to QA’ was not used on this occasion. However, a more general presentation was provided, which was out with the main theme, and was on the topic of animal experimentation. This meeting was sponsored by PMS, organized by Janette Milne and hosted by Peter Baxter and was attended by 17 delegates representing 8 organisations.

Peter Baxter (PMS) gave us a brief presentation and welcome to the meeting which provided us with a mini-history and overview of the structure, facilities and functions of the company.

Our guest speaker was Dr. Elspeth Scott, (Home Office) who gave us a presentation entitled, ‘Experimentation on Animals: Legislation and Inspection.’ This presentation provided us with the background for the legislation and the work of the Animals Scientific Procedure Inspectors. The European Directive required that the UK update its legislation in 1986 to ensure that experimental animal welfare was always being considered along with the scientific objectives. The operation of the Animals (Scientific Procedures) Act 1986 is the responsibility of the Secretary of State (SoS). The whole operation is governed by the Home Office. The inspectors themselves are either veterinarians or physicians normally with other scientific experience or qualifications. Their function is to assess applications for work and inspect and report any non-compliance with the Animals Scientific Procedure Act 1986. Another role for the inspectors is one of developing policy by providing advice to the SoS and to the scientists involved in the procedures, such as guidance documents. The whole purpose of the Act is to ensure any procedure carried out in animals must be done for a scientific purpose, properly justified and there is a requirement to prevent and reduce unnecessary animal suffering. Each programme of work is authorised by a project licence and this has a 5 year life span. In order to get such a licence the applicant must provide evidence of a cost benefit relationship, scientifically valid reasons for using the animals and a protocol of procedures to be undertaken. The programme must also be considered locally to judge that it is ethically sound. Each scientist who conducts the work must hold a personal licence and they are responsible for the welfare of the animals under their care. Inspectors have the duty to report non-compliances and advise on what action to take. Inspectors are also involved in the development of policy and the codes of practice for licensees. Elspeth also provided us with an approximate breakdown of inspector’s time, 45% assessment/advice, 45% inspection, approx 2000 inspections per year, (66% with no notice), 10% professional development and 5% general administration. From my experience, much the same allocation of time as a QA auditor.

Our first contributor to the main theme was Peter Baxter (PMS Ltd), delivered his paper on ‘QC in Biotechnology and GCPv.’ Within the biotechnology industry, such as vaccine production, QC can never be 100% due to costs or loss of material. The best that can be hoped for is quality confirmed! QC is too late for QA; Yes or No? The ‘Yes’ camp:- QC in production require Certificates of Analysis (CoA) to progress, The ‘No’ camp:- reliance on test result alone. It must be remembered that the CoA results are only as good as the method used in the determination. The example provided was that of the QC of gelatin, a lot depends on the method chosen. In ‘real’ QC there are the general accepted parameters such as SPC, Pareto charts, histograms, all measure ‘effect’. If you are involved in say the production of stem cell lines, if you don’t get QA right the products have failed.

In effect QC processes tell us QA systems have failed. When such a failure happens or is detected the whole batch fails. With biotech products there is normally no re-working possible so the batch must be scrapped. If for example a GCPv trial needs QC it fails - and the animals may be dead when you find out. The main QC failures are due to bad design of a trial or poor training and to a much smaller extent, fraud. The problem is one of dosing the animal in the field. Is the dosing correct? The only solution here is perhaps pre-packed doses and extensive training.

In the biotech area we are dealing with situations where there are no second chances and prevention is better than cure. It was suggested that 90% of the effort by all personnel should be focused on QA being up front. You have to make certain that there is time to look at and identify potential problems. From the GMP perspective, this system has matured, and is a stable system, with QA designed in all the way through the process, but there have been errors on the journey. GCPv must review the basics and adopt QA approach rather than QC one. Lack of a coherent QA function across the board should be considered a false economy.

Our second speaker was Richard Forster (Consultant) who delivered his paper ‘GMP in clinical trials: QC versus QA.’ This presentation focused on the differences between the directives around the world highlighting the differences in terminology used and various interpretations. Quality assurance defined QC and QC departments were typically QA except in the USA where the QA term is not formally used. The implication is that QA does everything but if that is the case, where does the QP fit in? The tradition of pharmacy within the manufacturing plant is still strong today in parts of Europe. There have been and are and results in some problems with delegation of duties and is as a consequence of high and sometimes low status of QA. Such situations may result in poor communication lines and will consequently have a bearing on process QA. The traditional QC approach is based on sampling, but with short clinical production runs more care is required over.
statistical justification for such methods of sampling. There often is no structured link to its intended clinical use, the certificate of analysis has a good like status and the concept of appropriate method validation is not always understood. The QC personnel are usually under pressure to produce the right answer quickly and in some cases the actions are already initiated assuming they will get the result they want! The QC’s challenges require are:

- Require QC or QA responsibilities for the data
- Adapting to novel applications and new technologies
- Increase their involvement with the process

The clinical trials directive changed everything for QC’s, ignorance is no longer bliss.

Richards view was that QC responsibilities should move towards:

- Relevant and validated test methods must be in use
- Detailed change control in operation
- Good communication links to clinical directors
- Ensure good science is used
- Provide the basis of an appropriate QC/QA system

QA has typically been the data review and the GP has been “legal” release. Most big pharma companies have operated a good QA/QC systems to meet US requirements. However, there is the current situation of part time contract QR; in today’s environment this is no longer really viable. Continuous monitoring is the way forward and policing is the wrong approach. It must be ensured that the key elements are in place and these are defined by the GP and that they are involved in the whole process. The traditional QC approach now probably exposes the GP to regulatory compliance problems. It is up to the GP’s to sort these systems out so that such situations do not occur. Finally it does not matter what we call what we do so long as we achieve fitness for purpose and patient safety.

The third presentation of the afternoon was delivered by Joanne Donald, (Charles River) entitled “GMP: To Check Or Not To Check, That Is The Question.” Joanne concentrated on the checks required with GLP computer system acquisition. In order to start identifying what to inspect/audit we need some definitions:

- Raw data: the original recorded observations and results
- Electronic record being any data used/stored in a computer system
- Hybrid systems that have a paper and an electronic record e.g. HPLC

The definition of that systems raw data must be defined within its SOP; this prevents problems after archiving the study if that definition is buried there. What is required to check stems is a decision tree approach whereby, three classes of data are looked at; electronic, hybrid and manual. Each can have multiple data entry routes each with its own QC requirements.

If the systems are validated or qualified, then only the components that are out with that validation, such as manual data entry, require to be subjected to QC checks. Where systems are not validated 100% QC checks are required and a GLP non-compliance statement may be required. The important thing to remember is for QA to have proper system documentation, develop and use checklists to ensure all aspects are covered. These checklists are best prepared during the final stages of validation so that as the important points are uncovered these can be included. This also allows for the production of guidance documents for the QA auditor to use when auditing systems. The aim is to audit based on the confidence you have on the QC data. As a general rule, validated systems require no QC checks (occasional spot checks); only the data in the report must be checked to ensure its integrity.

Spreadsheets used as data capture systems, again here we require our definitions, checklists and documents. Providing the spreadsheet is validated and the cells containing the formulae are locked. The QC system employed would only be concerned the manual data input. In summary you require a raw data definition, determine how the data gets into a computer system and then set up QC systems accordingly.

Our last session of the afternoon was delivered by Ewan Thomson, (Drug Development Solutions Ltd.) who gave us a presentation on, ‘GCP: Quality Systems and Data Management.’ Ewan provided an outline of what a clinical data manager does and how he ensures the quality of the data locked in a trial database. His theory was based on 3 pillars:

- Quality Staff
- Quality Documents
- Quality Systems

The first of these pillars is determined by training in the requirements of the trial and the implications of not completing the CRF properly. The data management staff must also be trained properly in order to function properly.

Quality Documents: in this context it is the way in which the CRF is designed. This is done by the data manager and reviewed by representative members of clinical staff who compare the draft design with the protocol requirements and refine the document to ensure total compliance. This is the design QC process. Once completed the document is sent to the sponsor for approval/amendment. Once approved the document can then be used as the design framework for the trial database. This database is then populated with some dummy data to confirm that internal validation rules are operational any errors noted are recorded in QC documentation and the database modified accordingly.

Quality Systems: Data entry systems are based on either direct import or manual methods. Data integrity is maintained by creation of two password protected copies of the empty database files. Each of these files is populated with trial data by two independent data input clerks. These files are compared and adjusted until congruence is achieved, and the documentation of this process forms part of the audit trail which is a hybrid system of paper and electronic systems. The data manager is now in a position to lock the database after consultation with the chief investigator and QA. The trial can be unblinded so that data processing can occur. Multiple QC checks are made to ensure that the tables which appear in the final report are still consistent with the source data. The problem is the balancing act they have to do regarding the quantity of QC to do as the law of diminishing returns applies and the cost mounts up. The lesson to be learned is that quality control on one study should not be used in isolation- but you must learn from your mistakes, and apply that knowledge to all other studies.

The steering committee wishes to thank all of our presenters who did an excellent job of giving a very good variety of contents, without any significant overlap. We would also like to thank Pentland Management System Ltd, for providing us with a venue, buffet lunch and Peter Baxter’s excellent rapourter skills, which were very much appreciated.

The next forum meeting is going to be a GLP workshop. This is planned for April 13, 2006.

If you wish to join the Scottish & Northern Regional Forum or have not received any recent e-mails from us it means that you are not registered or have provided an incorrect e-mail address. If this applies to you then please e-mail me at gogg@dsm.dundee.ac.uk and I will add you to the circulation list.

G.D. Ogg
There were two teasers in the last edition;

1) The answer was a lemon, but what was the question? - and what relevance does it have for us today?

2) For those with an interest in mathematics, we go back to Ancient Greek times - the island of Samos and subsequently Crotona in Southern Italy. Pythagoras (see inset) was an amicable man, his closest friend equally so. Assume they both lived, separately, on the same street as the rest of the Pythagorean Brotherhood - Pythagoras occupied number 284. What numbers might his friend and the rest of the Brotherhood have occupied? Given that each member of the Brotherhood occupied a separate dwelling, how many members were there in the Brotherhood altogether?

First - the answer to question 2

The Pythagoreans of ancient Greece were fascinated by whole numbers. One particular interest involved what is now known as amicable numbers - so the key in the question is the word ‘amicable.’

Amicable numbers come in pairs in which each number is the sum of the proper divisors of the other. The smallest such pair is 220 and 284 and the Pythagorean brotherhood regarded 220 and 284 as numerical symbols of friendship.

So if Pythagoras lived at 284 then his friend would live at 220.

The number 220 is evenly divisible by 1, 2, 4, 5, 10, 11, 20, 22, 44, 55, and 110 which add up to 284 whilst 284 is evenly divisible by 1, 2, 4, 71, and 142 which add up to 220.

So, if they all lived separately they would live at the following numbers: 1, 2, 4, 5, 10, 11, 20, 22, 44, 55, 71, 110, 142, 220 & 284. ...which makes 15 including Pythagoras & his friend! Tenuous I know, but it was Christmas.

The answer to question 1 relates to scurvy and what was possibly the first planned, controlled clinical trial by James Lind - 1st edition published 1753, 2nd edition published 1757.

 However ...

The focus of the April edition is ‘Corrective and Preventive Action’ and I’d like to throw my hat in the ring on that subject. We can possibly come back to the history of GCP at a later date - you might care to read about it in the mean time. Another example, earlier than Lind, sometimes quoted is “Comparison of two treatments of gunshot wounds; observations made between October 1537 and the end of 1538 ‘by Ambroise Paré.’

We can also look at Lind as an early innovator in food technology!... and no look at the history of GCP would be complete without an awareness of the Tuskegee Syphilis Experiment which ran for forty years between 1932 and 1972 and which elicited this apology from President Clinton to the eight remaining survivors on 16 May, 1997:

“The United States government did something that was wrong—deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all our citizens... clearly racist.”

‘Corrective and Preventive Action’

Moving on to ‘Corrective and Preventive Action’, I’d respectfully like to draw your attention to an incident in 1939 before the war started, when HM Submarine Thetis was undergoing sea trials in Liverpool Bay - unfortunately it sank with the loss of 99 men. 1 other man lost his life in the salvage process, so I’d like to dedicate this article to those men, their families & colleagues.

[Cammel Laird had built the 1,290 ton HM Submarine Thetis [motto “I bide my time”] launching her on the 29th June 1938. The initial trials were delayed because the forward hydroplanes had jammed, but on the 1st of June 1939 Royal Naval trials were finally due to commence. But the submarine was too light to dive and a survey of water within her various compartments was made - one check was to ascertain if the internal torpedo tubes were flooded.

On her trial day, Thetis carried 103 people, some 50 above her normal crewing level. There were 8 Naval Officers extra, some of them commanding their own submarines, coming along for the ride.
But a tragedy was about to unfold - the submarine sank and 99 people lost their lives. As stated above, Thetis was too light to dive, and a survey was made of water in various tanks on board. As part of this process, the Torpedo Officer, Lieutenant Frederick Woods opened test cocks on each of the torpedo tubes, these were designed to allow a small amount of water to flow if indeed a particular torpedo tube had had its bow door inadvertently left open. Woods opened up the test cock for Number 5 tube, but unbeknown to him it was blocked up by enamel paint, and no water flowed, indicating to him that this tube was empty of water, and its bow door shut.

[When a dockyard workman was about to paint with enamel paint, he had not first plugged this test hole….so promptly filled it up with paint, negating its safety role].

To further compound the problem, the layout of the bow door indicators was unusual - they were arranged vertically 1, 2, 3, 4, 5, with 5 at the bottom. The shut position for the Bow Door of Number 5 tube was in a different position to that of all the other torpedo tubes, this led to the rear door of Number 5 tube being opened.

[all appeared to be in order, no water dripping out when the test cock was opened and the bow door appeared to be closed]. Alas, not so… as a result of opening No 5 tube rear door, water flooded in from the open sea, causing the bow of the Thetis to plunge into the sea bed 160 feet below the surface. This left her stern stuck above the surface some 18 feet.

One of the themes at the Edinburgh BARQA Conference was moving the focus of QA away from the end product and focusing instead on Quality per se - bringing Quality & QA into the overall production process. There seem to be two main issues from the Thetis tragedy, one concerned with design ergonomics and the other with process.

When something has gone wrong, then with hindsight it is, relatively straightforward to identify what went wrong and then a corrective action can be put in place. That is indeed what happened with the Thetis. As a result of this particular incident, the rear doors of all torpedo tubes were fitted with a 'Thetis Clip' - a single dog clip, which stopped the door being opened more than a fraction. It allowed a very reduced flow of water, should the bow door be opened and once it became evident that the tube was empty of water, this safety clip could be overridden and the rear door safely opened.

However, I’d like to look at the issues from the Thetis in the current climate of ‘process improvement, error prevention & risk assessment’.

I had thought of using this as a training Module at work, but Quasar is likely a better forum. What were the major issues? … imagine you had been commissioned, either independently or by the Chief of Admiralty! Go back in time to 1938 before the incident happened, but knowing what did happen! Use your auditing skills to prepare a case for presentation to the Chief of Admiralty, in which you state your concerns at certain issues, fearing that if they went unattended they could result in something serious happening and what needed to be put in place to prevent this.

If you happen to be a manager (Chief of Admiralty) I’d like you to think how you would approach this type of document, what you would be looking for and how you would apply a risk assessment in today’s terms & then say whether the document is sufficiently persuasive to make you ask for change, thereby preventing the mistake.

Again as a manager, how would you demonstrate that your decisions had prevented a mistake happening? - tying in cause and effect. Would it be possible to convince you of a potential issue with one bow door indicator being designed differently to the others … or ensuring the test hole was not blocked after painting being considered as a critical step which required checking?

The very first time I read about the Thetis, I was moved by the sad nature of the incident. I think it shows how difficult it is to prevent errors happening as opposed to fixing after the event. Sometimes we come across issues which we feel intuitively could be improved - as QA, if we feel strongly then we have to keep chipping away until somebody sees the light. The exercise could alert us all as to how effectively to make an argument for change and how to persuade others into that line of thinking. I could do with some feedback to let me know whether I’m on the right track in attempting to make history relevant in today’s terms - contact me at barry.travena@covance.com and I’d be pleased to hear from you.

Someone at work suggested that when people hear the word history it may act as a “turn-off” to them….that may be the case, but it hadn’t occured to me. That statement probably tells me more about the individual than anything, but if it were to be true, then the underlying reason for attempting this series of articles wouldn’t be justified.

Personally, this year at work will see me adopting a policy of ‘back to basics’ - the basic principles of auditing. This will be a good exercise….and it’s all part of the cycle of change! I’m in some doubt at the moment regarding the value of the alternative viewpoint.

Barry Travena

Next issue: …who knows? Contamination? GCP History?

Maybe looking at ‘DNA testing mistakes at the Washington State Patrol crime labs from the Seattle Post-Intelligencer,’ or to what the appetite this slant on contamination taken from website http://coccine.org/cokebill.htm - but please don’t try this at work!

“The exchange of illicit cocaine for money by drug dealers is an everyday occurrence in cities in the United States. There is ample opportunity during the exchange, storage, and use of cocaine for paper currency to become contaminated. Because currency is exchanged frequently, it is likely that contaminated currency would be found in common use. We examined ten single dollar bills from several cities in the United States for the presence of cocaine. Individual bills were extracted with methanol (10 mL). Cocaine was purified from the methanol extract by solid-phase extraction (SPE). The SPE extract was analyzed by gas chromatography-mass spectrometry (GC-MS). Standard curves were constructed with new, uncirculated currency. Cocaine was identified qualitatively by full scan and quantitated by selected ion monitoring. Cocaine was present in 79% of the currency samples analyzed in amounts above 0.1 micrograms and in 54% of the currency in amounts above 1.0 micrograms. Contamination was widespread and was found in currency from all sites examined. Cocaine amounts were highly variable and ranged from nanogram to milligram amounts. The highest amount of cocaine detected on a single one-dollar bill was 1327 micrograms. These results indicated that cocaine contamination of currency is widespread throughout the United States and is likely to be primarily a result of cross-contamination from other contaminated currency and from contaminated money-counting machines.”

Quasar 39
# BARQA New Members

## New Members

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<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Country</th>
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<tbody>
<tr>
<td>Mr Frederic Clement</td>
<td>Ghent University Immunotrix</td>
<td>Belgium</td>
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<tr>
<td>Ms Stephanie Gilon</td>
<td>PPD</td>
<td>Belgium</td>
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<tr>
<td>Dr Rob Towart</td>
<td>Johnson &amp; Johnson Pharmaceutical R&amp;D</td>
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<td>Dr Marie-Odile Aldebert</td>
<td>Quintiles</td>
<td>France</td>
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<td>Ms Mitzi Dooley</td>
<td>Bayer Healthcare AG</td>
<td>UK</td>
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<tr>
<td>Dr Chitra Bargoje</td>
<td>Pfizer Ltd</td>
<td>India</td>
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<tr>
<td>Mr Vipul Doshi</td>
<td>Sun Pharma Advanced Research Centre</td>
<td>India</td>
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<tr>
<td>Ms Estie Baltner</td>
<td>Clinical Research Consultant</td>
<td>Israel</td>
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<tr>
<td>Mr Miles Lu</td>
<td>FMC</td>
<td>P R China</td>
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<tr>
<td>Ms Annelize Howell</td>
<td>Clinical Research Centres South Africa</td>
<td>South Africa</td>
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<tr>
<td>Mr Miguel Benade</td>
<td>Merck Farma y Quimica SA</td>
<td>Spain</td>
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<tr>
<td>Mrs Anne De Wever</td>
<td>Kinesis Pharma</td>
<td>The Netherlands</td>
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<tr>
<td>Ms Cigdem Ari</td>
<td>Sanofi Aventis</td>
<td>Turkey</td>
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<td>Mrs Sue Davies</td>
<td>Schering Health Care Limited</td>
<td>UK</td>
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<td>Mrs Samantha Felix</td>
<td>Allergan Ltd</td>
<td>UK</td>
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<tr>
<td>Mr Carlo Frate</td>
<td>Veterinary Laboratories Agency</td>
<td>UK</td>
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<td>Dr Joanna Galea-Lauri</td>
<td>Institute of Child Health</td>
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<td>Mr Andrew Hare</td>
<td>GlaxoSmithKline</td>
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<td>Mr Steve Lomax</td>
<td>Renovo Ltd</td>
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<tr>
<td>Mrs Rachel Mackay</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>Mrs Julie Sinclair</td>
<td>Royal Wolverhampton NHS Trust</td>
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<td>Mr Bryan Stack</td>
<td>Covance Laboratories Ltd</td>
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<td>Mr Stephen Squirrell</td>
<td>Xenova Research Ltd</td>
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<td>Mrs Jane Williams</td>
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<tr>
<td>Miss Catherine Willmore</td>
<td>Covance CRU</td>
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## New Affiliate

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<tr>
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<tr>
<td>Mr Johan Birgersson</td>
<td>Pfizer</td>
<td>Sweden</td>
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<tr>
<td>Mr Ian Patterson</td>
<td>Novartis Pharmaceuticals UK Ltd</td>
<td>UK</td>
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<tr>
<td>Mr Kevin Polhill</td>
<td>Avecia Ltd</td>
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<td>Mr Steve Smith</td>
<td>S C Johnson</td>
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## New Associates

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<tr>
<th>Name</th>
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<tr>
<td>Mr Guy Houben</td>
<td>Johnson &amp; Johnson Pharmaceutical R&amp;D</td>
<td>Belgium</td>
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<tr>
<td>Mr Hans Mols</td>
<td>Johnson &amp; Johnson Pharmaceutical R&amp;D</td>
<td>Belgium</td>
</tr>
<tr>
<td>Mrs Vanessa Ruymen</td>
<td>Johnson &amp; Johnson Pharmaceutical R&amp;D</td>
<td>Belgium</td>
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<tr>
<td>Dr Claudia Hartig</td>
<td>Schering AG</td>
<td>Germany</td>
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<td>Mrs Louise Baker</td>
<td>Precision Histology International</td>
<td>UK</td>
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<td>Dr Kerry Bunyan</td>
<td>Charles River Laboratories</td>
<td>UK</td>
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<td>Mr Peter Chandler</td>
<td>Huntingdon Life Sciences</td>
<td>UK</td>
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<tr>
<td>Miss June Collington</td>
<td>Isolagen Europe Ltd</td>
<td>UK</td>
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<tr>
<td>Mr Paul Davidson</td>
<td>Charles River Laboratories</td>
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<td>Mr Darlington Eke</td>
<td>Nonstop Pharmaceutical Services</td>
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<td>Miss Catherine Fitzharris</td>
<td>Covance Laboratories Ltd</td>
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<td>Miss Tracy Freeman</td>
<td>Covance Laboratories Ltd</td>
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<td>Ms Celia Gibson</td>
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<td>Miss Elizabeth Harris</td>
<td>Wickham Laboratories Limited</td>
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<td>Mr Russell Harrison</td>
<td>Parexel International</td>
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<td>Mr Ben Jackson</td>
<td>Huntingdon Life Sciences</td>
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<tr>
<td>Miss Jeanette Langstone</td>
<td>Cambridge Antibody Technology Ltd</td>
<td>UK</td>
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<td>Ms Penny Lisney</td>
<td>3M Health Care Ltd</td>
<td>UK</td>
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<tr>
<td>Mr Han Low</td>
<td>Harlan UK Ltd</td>
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<tr>
<td>Miss Rebecca Lubi</td>
<td>Pfizer Global Research &amp; Development</td>
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<tr>
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<td>NAPP Pharmaceutical Ltd</td>
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<td>Mr Andrew Upsall</td>
<td>Covance Laboratories Ltd</td>
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<td>Ms Sharon Wolfe</td>
<td>Quintiles Laboratories</td>
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Introducing the BARQA New Member Welcoming Scheme

From the Membership Needs Working Party, during 2005, it was established that some new members experience difficulties meeting and introducing themselves to other members when everyone else appears to know each other, particularly at meetings. This may be a particular issue for new members who are the only representative from their organisation. To meet the needs of new members, a Welcoming Scheme is being introduced whereby new members are assigned a current member to welcome them to the organisation, ensuring they are aware of BARQA services and providing a key point of contact for the new member.

Establishing a Welcoming Group
All members of BARQA are invited to join the Welcoming Group. In future, the option to become or remain a member of the Welcoming Group will be included on the annual membership renewal form.

The role of the ‘welcomer’
- Make contact with the new member.
- Make sure they know about BARQA’s activities.
- Make sure they know how they can contribute to working parties, events and publications.
- Make sure they know how to contact key individuals within BARQA who are active in their area of interest.
- Be available to be contacted by the new member for their first year of membership.
- Take up opportunities to meet face-to-face at BARQA events which both ‘welcomer’ and new member are attending.

Please contact the BARQA Office if you would like the opportunity to welcome new members to the organisation.

Linking new members to the Welcoming Scheme
Once the Welcoming Group has been established, hopefully in the next few months, all new members, including those who joined during 2005, will be invited to join the scheme. The scheme is optional. The Office will link up new members with a member of the Welcoming Group, taking into account the field of activity and geographical location, and issue a letter to both the new member and assigned ‘welcomer’ including contact details of both individuals.

Maintenance of the scheme
Both the Association Manager and the Ordinary Board Member with this accountability will conduct an annual assessment of the scheme.

Rachel Hodges and David Weller

The Membership Needs Working Party’s proposal to form a monitoring group to monitor the Board’s progress on the party’s proposed initiatives outlined in the green paper presented to the Board in 2005 was ratified at the Board meeting held on 19th February 2006. The monitoring group will meet within a month of the Board meetings to review progress and will update the membership through QUASAR.

Zelda Carr
**The Lighter Side**

When you think about the differences between work and prison, maybe prison isn’t so bad...

**In Prison...** You spend the majority of your time in an 8 x 10 cell.
**At Work...** You spend most of your time in a 6 x 8 area.

**In Prison...** You get three meals a day.
**At Work...** You get a break for 1 meal and you have to pay for it.

**In Prison...** You get time off for good behaviour.
**At Work...** You get rewarded for good behaviour with more work.

**In Prison...** A guard locks and unlocks all the doors for you.
**At Work...** You must carry around a security card and unlock and open all the doors yourself.

**In Prison...** You can watch TV and play games.
**At Work...** You get fired for watching TV and playing games.

**In Prison...** You get your own toilet.
**At Work...** You have to share.

**In Prison...** They allow your family and friends to visit.
**At Work...** You cannot even speak to your family and friends.

**In Prison...** All expenses are paid by taxpayers with no work required.
**At Work...** You get to pay all the expenses to go to work and then they deduct taxes from you salary to pay for prisoners.

**In Prison...** You spend most of your life looking through bars from inside wanting to get out.
**At Work...** You spend most of your time wanting to get out and go inside bars.

**In Prison...** There are wardens who are often sadistic.
**At Work...** They are called supervisors.

**In Prison...** You have unlimited time to read e-mail jokes.
**At Work...** You get fired if you get caught.

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Now get back to work!
The Publications Committee needs active, enthusiastic, innovative and creative members to join the team to help drive forward and deliver:

- The Association’s publications specifically, Quasar Magazine, the web site and technical publications/booklets
- Communications within BARQA on matters relating to publications
- Publication information which serves the needs of the membership

If you feel that would like to be part of the team please contact Judith Elliott by telephone on 01344 414708 or by email Judith.elliott@syngenta.com

We would be pleased to welcome both UK and overseas members to the committee
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- Clinical Quality Assurance - South/South West
- QA Development - South East
- Senior Clinical QA Auditor - South/South West
- QA Auditor - East Anglia
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Submit articles for ‘Quasar’

If you would like to submit an article on the theme Risk Management, future themes or for a topic you feel would be of interest please contact the Editor or one of the Sub-Editors (details on page 43)