FEATURED ARTICLES

The Bribery Act

Data Integrity and Detection of Fraud in the Audit of Manual and Automated Systems

Global Digital Forensics Case Study – Drug Diversion

Russian Roulette; Why do Researchers Risk All to Commit Fraud?
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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.
The theme for this Edition is ‘Fraud and Scientific Misconduct’. There has been a good variety of articles submitted, spanning seven themed articles:

- ‘The Bribery Act’ by the Chartered Quality Institute explains what it is, when it came into force, what your organisation needs to do, what the risks are and the guidance available.
- ‘Data Integrity and Detection of Fraud in the Audit of Manual and Automated Systems’ by Iain McPhee summarises the quality and compliance issues that may be relevant to the data integrity and fraud, and the indices an auditor should be aware of and the safeguards that can be put in place to encourage good quality practice.
- ‘Fraud and Misconduct in Clinical Research’ by Barney Horne and Nicky Dodsworth gives an in-depth overview of types of fraud and misconduct, motivation, detection, examples of red flags, investigations, reporting and prevention.
- ‘Counterfeit Products in the Clinical Supply Chain’ by Matilda Street covers definitions, the extent of the problem, potential impacts, entry into the supply chain, raw materials, the comparators and global activities.
- ‘Fraud and Scientific Misconduct - Why does it happen, and what can we do about it?’ by Martin Bridgstock gives his experience from the school of Biomolecular and Physical Sciences for the main reasons for misconduct and what can be done in terms of correction and prevention.

Also in this edition, Hi Society features the Danish Quality Assurance Society (DKGI), committee and working party updates and the board biography of Mark Goodwin, Chairman of the GLP Committee.

Sadly, Joy Eldridge, former Publications Committee Chairman, has now left the Committee and we would like to thank her for all her hard work and enthusiasm over the years. We welcome two new members who volunteered themselves to the Publications Committee, Jan Ball and Jon Read and we all look forward to working with them.

Did you know that current and past issues are available electronically on the BARQA website. They can be found in the members’ only area box on the right hand side of the screen. There is also a handy Quasar articles directory to help you pin point articles contained in past editions.
Dear Friends,

Welcome to the final edition of Quasar for 2011 and here are a few items I would like to highlight.

CONFERENCES

The BARQA Annual Conference was held last month and I would like to thank all BARQA members who attended this year. It was a superb conference and we still welcome any further feedback you have regarding this event. Thank you for your support. My thanks also go to the 2011 Programme Committee, chaired by Sue Anderton, for an excellent programme of presentations and discussions and to the BARQA office staff for delivering another conference to such high standards.

An article summarising the Conference, the Annual General Meeting and the new BARQA Board will be published in the next edition of Quasar in January.

The 3rd Global QA Conference is now just around the corner and I would like to encourage you to consider registering for this special event. This time the conference is being hosted by JSQA in Kyoto, Japan, from the 13th to 16th November 2011. Please take a look at the conference website (www.3rdgqac.com) for more information about the conference and the programme.

RECENT DEVELOPMENTS

There have been some recent personnel changes in the European Quality Assurance Confederation (EQAC) which is derived from national Quality Assurance societies based in Europe (www.eqac.eu). Anders Wichman is now the new secretary, previously held by Nigel Dent, and Martha Byrne has taken the role of rapporteur. The BARQA office has also offered to assist EQAC with administrative aspects of the organisation.

The new Quality Systems Workbook has recently been published by the BARQA Outreach Working Party and is available on the BARQA website. There is also an article featured on page 40 of this edition. The document provides excellent guidance for organisations wanting to understand, develop and implement an improved quality system, based on the principles of quality. It is a significant output from the Outreach Working Party and a valuable addition to the catalogue of BARQA booklets already available.

FORTHCOMING ACTIVITIES

Hopefully you will have received communication from BARQA relating to the ‘Red Tape Challenge’. It is a UK government initiative to reduce the burden of regulation. It enables you to comment on UK government regulations. Every few weeks the regulations will be split into themes affecting one specific sector or industry and will be published on the ‘Red Tape Challenge’ website. All these regulations will be open for your comments.

The MHRA will be part of the ‘healthy living and social care’ theme and it is expected that this aspect will be available for comment early in 2012. (www.mhra.gov.uk/NewsCentre/CON126048).

Best Wishes

Rachel
Mark is Director of UK GLPQA at GlaxoSmithKline based at Ware in Hertfordshire. He is responsible for the UK GLP Quality Assurance Programme and for leading the UK GLP QA team. Mark was a founder member of the BARQA GLP Committee and is the current Chairman. He is also a member of the (UK) GLP Consultative Committee and the newly established OECD Discussion Group.

Mark completed a degree in Applied Biology at Liverpool Polytechnic. As this was a sandwich course he spent his third year in Norwich at the Coypu Research Laboratory. The Laboratory was set up to control the coypu population that was becoming well established following closure of coypu fur farms in East Anglia. Mark thoroughly enjoyed his spell at the laboratory and was relieved to avoid being bitten - the coypu has 6cm incisors!

Following his degree course, Mark worked at Toxicol Laboratories in Ledbury. He was a technician involved in several areas of work including pyrogen testing and abnormal toxicity testing; despite enjoying the lifestyle, work and camaraderie he decided to move on into the field of GLP Quality Assurance. Mark gained QA experience at Life Science Research (back to coypu territory in East Anglia) and SmithKline & French before moving to Glaxo Group Research in 1988. Working for a CRO exposed Mark to great diversity in terms of study types and procedures. This created a sound platform for a move into the pharmaceutical industry. Mark gained knowledge of pharmaceutical development initially at SmithKline & French at the Frythe site where he also added to his QA expertise. After three years, Mark moved to Glaxo Group Research and experienced two mergers that created Glaxo Wellcome and then GlaxoSmithKline. The most recent merger meant that Mark, although based at Ware, spent considerable time back at Frythe until the site was recently closed. Mark became Director of UK GLPQA in August 2010 and is enjoying this challenging role. He gains much satisfaction from the great teamwork within QA and also from partnering with the business groups.

In terms of BARQA involvement, Mark is the current Chairman of the GLP Committee (his second spell in this role, as he was Chairman between 1997 and 2001). He was an industry representative at the OECD Consensus Workshop on Multi-site Studies and is a current tutor on the BARQA ‘Managing Multi-site GLP Studies’ course. Mark participated in the 2008 OECD GLP event in Italy at which monitoring authorities, receiving authorities and test facilities presented topics of GLP interest. Mark was also a stakeholder during development of the MHRA risk-based inspection strategy.

Outside of work, Mark is a keen runner and a member of Fairlands Valley Spartans Running Club. He regularly participates in races ranging from 5K to marathons; he is pleased that he has achieved two sub four-hour marathons from the three he has run. Mark also enjoys football, as a spectator rather than a player these days! He supports Everton and his home town club, Rochdale.
FEATURE

The Bribery Act

CHARTERED QUALITY INSTITUTE
With the much discussed Bribery Act now in force, what do you need to know?

What is the Bribery Act?
The new act covers bribery which takes place in the UK and overseas, by employees and third-parties employed by your organisation.

An organisation could be liable if a senior member of staff, such as a managing director or CEO, commits a bribery offence, such as offering, promising or giving a reward to induce a person to act improperly or accepting a bribe.

An organisation could also be liable if it fails to prevent someone who performs services for it, such as an employee or someone employed as an agent, from paying a bribe specifically to get business, keep business, or gain a business advantage for the organisation. However, it is very unlikely that an organisation will be liable for the actions of someone who simply supplies goods to them.

When did the act come into force?
The Bribery Act 2010 came into force on 1st July 2011. This followed the government’s announcement that implementation of the act would be delayed until three months after the guidance from the Ministry of Justice was published to give businesses time to consider its implications and to take any further steps required to design and implement compliance programmes.

What defence could our organisation make if challenged under the act?
Your organisation would need to demonstrate that you had adequate procedures in place to prevent bribery. What counts as adequate will depend on the bribery risks your organisation faces and the nature, size and complexity of your business. This would be a viable defence and might help you to avoid prosecution.

What are the risks?
Many organisations will face little or no risk of bribery, especially if their business is undertaken primarily in the UK. If you operate overseas, you should consider the particular country you want to do business in, the sector that you work with, the value and duration of your project, the type of business you want to do and the people you employ or work with to carry out your business when assessing the risks involved.

My company is based outside the UK. Will the Bribery Act still apply?
Yes – all that is required for the law to apply to an organisation is that it carries out some or part of its business in the UK. This could be done via a subsidiary, a branch, an agent or some other connection with the UK.

What guidance regarding the act is available?
The Ministry of Justice has produced a quick start guide that documents the steps a business should take to assess risk and implement procedures. It can be found at: www.justice.gov.uk/guidance/docs/bribery-act-2010-quick-start-guide.pdf

The Directors of the Serious Fraud Office and Department for Public Prosecutions have also published joint guidance on prosecutorial decision-making under the act to coincide with the Ministry of Justice guidance. You can download the guidance at: www.sfo.gov.uk/media/167348/bribery%20act%20joint%20prosecution%20guidance.pdf

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Pre-clinical, clinical studies and pharmacovigilance activities generate data. How data is generated and handled is critical and the integrity of data is increasingly the focus of audits and inspections. This is shown by the increasing number of regulatory agency inspection observations related to data integrity issues (ref. FDA inspection warning letters).
There must be assurance that data is both reliable and accurate from collection at source to the endpoint of reporting. For GxP and GPvP, there are clear requirements for Good Documentation Practice and for computer system standards, e.g. CFR 21 part 11 in the USA or comparable standards elsewhere. Systems assuring data integrity provide the basis for trustworthy data. Trust but VERIFY!

**Definitions**

**Data:**
- Can be defined as facts or results of firsthand original observations
- Can exist in a variety of forms, for example as numbers or descriptive text recorded on paper or as bits and bytes in electronic form
- Can be in several formats, for example as original records or certified copies of original records, in manual or electronic format

**Documentation:**
- Provides objective evidence of the conducted activities
- Is recorded information, manually written or electronic, that establishes specifications or processes, directs work and collects the records which ensure compliance with quality systems
- A correctly prepared document is permanent, legible, accurate, consistent, clear, truthful and appropriately approved

Documentation in studies includes:
- Protocol and Report
- Study Case Report Form [record]
- Ethics Committee approvals, where appropriate
- Regulatory authorisation or notification of protocol
- Informed consent
- Study/laboratory/technical procedures
- Monitoring visit reports
- Laboratory data records
- Other documentation needed to reconstruct the study, for example communication records, sample storage records, test item accountability records, etc.

Documentation in PV includes:
- Adverse Event Report, SOPs and proforma for collection of key information
- Call centre records
- ABON* causality assessments

**Fraud:**

Fraud is the intentional falsification of results, the knowing and intentional recording or reporting of incorrect information, for example where failed requirements are made to appear acceptable during reporting. This is distinct from unintentional improper practice, the scientifically unsound or technically unjustified omission, manipulation or alteration of procedures or data, making results appear acceptable.

At audit, a claim of fraud must be fully supported by conclusive evidence, separate from scientific/research misconduct or improper practice. If there is doubt regarding the veracity for a claim of fraud, there are generally other critical audit observations to show systemic failure at an audited site.

**Data Integrity**

*Data Integrity is the condition existing when data is unchanged from its source and has not been accidentally or maliciously modified, altered or destroyed*

**Data Integrity:**

*Data Integrity is the condition existing when data is unchanged from its source and has not been accidentally or maliciously modified, altered or destroyed* [National Information Assurance Glossary]. Validation ensures that equipment, instrument or system in use measures what it should measure and that those measurements are accurate, precise, specific, linear and robust over a stated range.

**Audit Findings**

There are recognised triggers or ‘red flags’ that can be an indicator of data integrity issues. During auditing the types of general observations an auditor will be alert to include:

- Back-dating of data entries
- Omission of data
- Edits to data and incorrect changes to data
- Improper recording practices, for example original entry obscured
- Fabrication of data
- Similarities/differences in handwriting for individuals

**Computerised Systems**

Electronic data are original test records and documentation created, read, stored or managed by means of computerised systems (containing a microprocessor) and/or data stored on digital media.

In computerised systems the ability to detect data integrity issues including fraud is more problematic than in manual paper based systems. Therefore additional controls, including computerised system validation (CSV) are required to assure the integrity of computerised records. Study protocols should identify steps where a computerised system will be used; SOPs must be in place for creation, modification, maintenance and transmission of electronic records.

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*ABON Definition
A The medicine probably caused the reaction observed
B The medicine possibly caused the reaction observed
O There is insufficient information to judge if the medicine caused the reaction observed
N The medicine probably did not cause the reaction observed.*
FEATURE

Iain entered QA with GLP in veterinary safety studies, he developed in GCP QA with a key role in interpretation of directives and VICH guidelines; including leading the BARQA publication on the monitor’s role in GCP. Joint publications with SQA AHSS followed.

Iain is the Global e-Compliance Manager for Novartis Animal Health, his responsibilities include data integrity assurance at Novartis and for third party suppliers.

A member of BARQA Animal Health Committee, he is a past BARQA Board member and committee chairman.

For computer systems, access should be restricted to authorised individuals with identification unique to each individual, for example with passwords or biometric data. If passwords are used these can’t be shared and the system should prompt for the password to be changed on a frequent basis.

In addition to the recognised triggers/red flags above that are common to paper and automated systems, computerised systems additionally have the following red flags:

- Inadequate systems to ensure full data integrity, e.g. lack of SOP coverage
- A lack of or improper computerised systems practices:
  - Audit trails (internal computer record of who does what, when and why) not present, inactivated or not readable
  - No periodic review of audit trails and user access
- Access to data is not controlled
- Non-compliance with regulations e.g. equipment not CFR 21 part 11 compliant [FDA regulation]
- Qualification gaps and issues

Particular care is required with hybrid systems, those that depend on the integration of both manual and automated systems; for data transcribed from patient charts to data collection forms, the electronic data must be stored and accessible during the defined archiving period. Computer-generated and time-stamped audit trails will be present for data entry, additions and alterations including reason, person, and the original information. There should be no programming features to automatically enter data when a field is by passed.

External security measures, such as limited access, etc. should be established. There must be sufficient backup and recovery procedures, backups should be stored in a secure location (e.g. off-site). Change control procedures with impact assessment and revalidation if necessary are required.

Personnel responsible for computerised systems must have appropriate education, training and experience.

Conclusion

Across GxP and GPvP, the document type may be different but the expectations for data integrity are the same, to ensure confidence in the reliability, quality and integrity of electronic and manually recorded data and documentation.

This article has summarised the quality and compliance issues that may be found relevant to data integrity and fraud, and the indices an auditor should be aware of and the safeguards that can be put in place to encourage good quality practice. It is my experience over many years that the precursor to major data integrity issues and fraud is poor management and an organisational culture that does not support quality, often associated with the expectation of an unrealistic workload.
Global Digital Forensics Case Study – Drug Diversion
Case Background
A pharmaceutical company began receiving complaints from its representatives in certain geographical areas that sales of normally high volume drugs were slowing down considerably. The company's internal security department, as well as the security departments of its major distributors, began an investigation. The results of the investigations led these security professionals to believe a significant amount of the company's product was being diverted from foreign countries into the United States and sold through smaller distributors who specialised in sales to locally, privately owned pharmacies and dispensaries within nursing homes.

The diversion activities were immediately reported to the local authorities in the regions as well as to the FDA. An investigation was immediately launched and millions of dollars of diverted drugs and repackaging equipment was seized from several locations, including the warehouses of fully licensed pharmaceutical distributors. Along with the diverted product, the computers and other electronic equipment was also seized.
The seizure went smoothly and the company was satisfied, as were investigators from the FDA and local law enforcement. However, the case was severely hindered by the fact that the majority of communications between the principals of the distribution companies (foreign nationals) and the foreign suppliers was conducted by email. There were also virtually no paper records on-site.

Global Digital Forensics Involvement
The company called in Global Digital Forensics (GDF) and working in cooperation with the local authorities as well as with the FDA and US Attorney's Office. GDF was able to commence computer forensic analysis of the computers seized at the pharmaceutical warehouses and provide the information and artefacts recovered during the computer forensic analysis to the US Attorney's Office.

GDF dispatched a mobile computer forensic lab and along with investigators from the US Attorney's Office, created forensically sound copies of the hard drives seized from the warehouses to be used to conduct the computer forensic analysis. Strict chain of custody was maintained and the computer forensics were conducted under the supervision of the US Attorney’s Office following all accepted computer forensic methodologies.

It became obvious that the investigation would be delayed until one of the labs, cleared some high priority cases and could dedicate the time required to forensically analyse the computers from the seizure. Time was of the essence and everyone knew that the computer forensics had to begin immediately if the diversion was to cease and the case successfully prosecuted. The suspects claimed they were reshipping the drugs outside the US (a legal practice) and had shipping bills that appeared to back this statement up. Without the documentation on the computers it was almost assured that the US Attorney’s Office would drop the charges.
The Findings

GDF computer forensic specialists were able to decrypt and extract a wealth of information from the systems that were forensically analysed. By conducting a complete computer forensic analysis of all the data the hard disks contained, GDF were able to provide documentation showing that the diverted drugs were being purchased from distributors in Europe and from Canada and being shipped to the US in what appeared to be legitimate transactions.

The computer forensic analysis also showed that the distributor had purchased equipment to unwrap the foreign drugs as well as repackaging equipment, all signs of a legitimate drug repackaging and exporting company.

GDF’s computer forensic analysts were also able to extract documents showing that the owners of the distributors also controlled several pharmacies in the area, as well as several nursing homes and assisted care living facilities in the area, all of which appeared to purchase drugs from the distributors. There were also many invoices for custom vitamins shipped to another distributor just two buildings away that also appeared to be controlled by the suspects.

The Outcome

Using the digital evidence the computer forensic specialists gathered, along with the physical evidence, the US Attorney was able to prove:

1. The distributor was purchasing drugs from foreign sources to be sold within the United States
2. The distributors were engaged in drug diversion for over 10 years
3. The distributor was repackaging vitamins manufactured to appear the same as the prescription drugs and selling and shipping them to Asia
4. The distributor was operating unlicensed pharmacies and nursing homes

The company sustained over 13 million dollars a year in lost revenue and the suspects distributed millions of dollars in counterfeit drugs throughout Asia, potentially endangering the lives of hundreds of innocent people.

The suspects were convicted and sentenced in the United States and are being investigated in five other countries.
My colleagues and I work in the specialist field of investigating fraud and misconduct in biomedical research. We are often asked why such fraud is committed. To answer this conclusively one must have the mindset of a fraudster; why one would commit any sort of fraud is actually beyond my comprehension. But there do seem to be common themes when one seeks some sort of justification.
Peter Jay, who with Frank Wells founded MedicoLegal Investigations (MLI) in 1996, lists greed, need and breed as the main tempters. The first is self-explanatory, the second category includes addiction to drugs, alcohol and gambling and the need to pay for them, and the third includes the fact that some achieve an adrenaline buzz by lying, cheating and deceiving in order to get something for nothing. Other major motivators include arrogance (“I’m too clever to be caught”) and the need to achieve publications to further career aims.

Whatever the reasoning, and we must be clear, fraud is never accidental, but always done with intent or recklessness. Those who commit it and are found out find themselves without employment. Career, family, future all ruined.

Greed
This does not seem an obvious reason as the fee per patient in a pharmaceutical industry sponsored study starts at perhaps £1–£2000. Certainly not, one might think, worth risking a career for. However if 20 ‘imaginary’ patients are fraudulently included in a study and an investigator takes on three studies for different companies, the figures look more attractive and of course many studies bring a fee of much more per patient. MLI has dealt with a few fraudsters who have exceeded £250,000 in fees for work that they did not actually do and one who amassed well over one million pounds. The following case illustrates greed, although the perpetrator was never investigated. A Clinical Research Associate (CRA) in my department in a Contract Research Organisation was concerned that all did not seem right at a busy site. He asked the study nurse how she measured heart rate and learnt that she counted the radial pulse for 15 seconds and multiplied by four. Yet when she was shown that very few of her patients’ heart rates were actually divisible by four she broke down in tears. The Principal Investigator (PI) seemed unable to turn away studies, so the unit had many studies with insufficient research staff, and she was unable to keep up with all the tests in all the protocols on all the patients. So she made up some of the data, justifying it by saying that she ‘never made up important data. That’s all real’. The greed of the PI in the face of insufficient staff put patients’ lives at real risk. He was pre-eminent in his field and the proposed lead author when the study came to publication.

Adrenaline Buzz
Perhaps we see this in the case of Malcolm Pearce. A respected UK gynaecologist, Pearce reported the successful reimplantation of an ectopic fetus in 1994. It was due largely to a whistleblower that it later emerged that there had been no such operation performed.

Pearce was one editor of the journal in which the report was published and the editor in chief, Professor Geoffrey Chamberlain, was his head of department and a co-author. Chamberlain’s role in the work is not known, but he was quoted by a newspaper as saying, “The head of the department’s name is always put on reports out of politeness. I was not part of this work, but I have always trusted Mr Pearce”. When the fraud was discovered the careers of both the men were effectively ended. Did Pearce risk all for the ‘buzz’ when he must have known the likelihood of being found out?

‘fraud is never accidental, but always done with intent or recklessness. Those who commit it and are found out find themselves without employment.’
Jane qualified in medicine in 1976 and joined the pharmaceutical industry in 1985. In 2001 she was awarded a Master’s degree in Medical Law. She now provides medical and legal expertise to pharmaceutical companies, and is Consultant and Medico/Legal Adviser to MedicoLegal Investigations Ltd, a UK-based company investigating alleged fraud and misconduct in clinical research.

Jane is immediate past Chairman of the British Association of Pharmaceutical Physicians, and was until 2006 Registrar of the Faculty of Pharmaceutical Medicine.

Arrogance

I believe the majority of cases of detected fraud fit here. The longer a fraudster continues, the more arrogant he or she becomes and there seems to be a real sense of superiority of intelligence; ‘too smart to be found out’. Very often we find that the investigator is well known and well respected, so nobody can conceive that he could possibly be other than honest.

We disproved this in the case of Tonmoy Sharma, a key opinion leader in psychiatry. He used the designation of Professor, to which he was not entitled, and when he was unable to produce Ethics Committee (EC) approval for an investigator-initiated study he was performing, he claimed that as it was so similar to one he’d carried out the previous year he did not need to reapply. He also combined protocols from two sponsor studies, using tests from one study on the subjects in the second without EC knowledge or patient consent, with the apparent intention of writing a paper using all subjects. His arrogance extended to defending himself, unsuccessfully, at a General Medical Council disciplinary hearing.

Vasu Agrawal also thought he would not be suspected of research fraud. As a General Practitioner he had the trust of his patients, so when recruiting for a hormone replacement study he did not tell his subjects that they were in a trial, but forged their consent signatures and gave them medication from his desk drawer. He was not too clever to be caught by an observant CRA and a forensic handwriting expert.

Pressure to Publish

William McBride was an Australian obstetrician and the first to report that Thalidomide was causing limb deformities in babies born to women who had taken it during early pregnancy. Some 20 years later, he published research showing that another drug for sickness in pregnancy caused birth defects in rabbits. The drug was withdrawn, but no researchers could reproduce his work. With the help of a whistleblower, it was shown that McBride had altered research results, and there was no teratogenicity. McBride was found guilty of scientific fraud by a medical tribunal and removed from the Medical Register. His reason for the fraud was that he had been under heavy pressure to publish papers. He knew that with his Thalidomide history, publication of such results would be guaranteed.

Conclusion

It is hard for the majority of us to understand the rationale behind fraud although it helps to have colleagues like mine who have worked for many years on police investigations of fraud of all types. Because most investigators are totally honest and trustworthy, it is easy to fall into the trap of believing that all are. However, to do so does disservice to our research subjects, our own industry and indeed all those honest trialists. Several of those named above were well-respected and key opinion leaders. They were seen as being above suspicion, yet they were all found guilty of fraud. Public image can be deceptive; but we must always be alert to the possibility of fraud.
Fraud and Misconduct in Clinical Research

BARNEY HORNE AND NICKY DODSWORTH
Introduction

Fraud and misconduct in the research community occur more often than we would wish to believe. While it is impossible to provide a definitive figure for the frequency of its occurrence, surveys provide us with consistently (and perhaps surprisingly) high estimates. A meta-analysis of such surveys showed that 2% of scientists admitted to having fabricated, falsified or modified data or results at least once, and up to 34% admitted other questionable research practices, such as plagiarism.

Interestingly, the analysis showed that misconduct was reported more frequently by medical/pharmacological researchers than others. Considering that these surveys ask sensitive questions and have other limitations, the authors concluded that this is likely to be a conservative estimate of the true prevalence of scientific misconduct.

As if the frequency of fraudulent research was not concerning enough, the impact on affected individuals and the research community can be profound. At the very least, a single isolated case of fraud – say a clinical investigator fabricating a limited number of data points in a trial – will result in considerable costs to the pharmaceutical sponsor company and disciplinary consequences for the offending investigator. The costs to the company include additional resource for investigation and reporting of the fraud and possibly additional rework costs to repeat the fraudulent aspects of the research.

At worst, fraudulent clinical research affects the validity of data and impacts on the dignity, rights, well-being and safety of research participants. Some cases have involved serious abuse of participants, most notably the Tuskegee Syphilis Study, American radiation experiments and the cases described in the Pappworth’s seminal study. It was cases of such gross misconduct that led to the development of Ethics Committees and the introduction of clinical trial legislation.

Such ethical and other controls have nowadays made these extreme abuses a rarity, but clinical investigators who fraudulently include ineligible subjects into a clinical study still put the safety of these subjects at risk. Furthermore, widespread fabrication of data, if undetected, could result in the registration of a medicinal product based on unreliable data, thereby endangering the health of future patients.

Types of Fraud and Misconduct

There are a variety of definitions of fraud and scientific misconduct. Often, the terms ‘fraud’ and ‘misconduct’ are used interchangeably. Generally, fraud describes acts of omission and commission, consciously not revealing all data and consciously altering or fabricating data. Such falsification of data can occur at any stage of the research process, from initial design through to reporting results. Fraud does not include honest errors or differences in opinion and the usual definitions include an element of intent. Repeated non-compliance with the study protocol and GCP may be considered as an example of misconduct, although the end result may well be similar to deliberate fraud.

Wikipedia presents a useful and accessible definition from which a short summary has been provided below:

**Fabrication** is the publication of deliberately false or misleading research. This can be omission of critical data or results for example, the reporting of only positive outcomes and none of the adverse outcomes. Equally, statements can be made that are entirely unsubstantiated. Another form of fabrication is where references are included to give arguments the appearance of widespread acceptance, but are actually fake, and/or do not support the argument.

**Plagiarism** is the act of taking credit (or attempting to take credit) for the work of another. This is probably the most common type of scientific misconduct. Misconduct is not just aimed at those who do not list authorship, but also includes those who have not made substantial contributions to the research and claim it for their own. Suppression of significant findings is also considered a form of misconduct.

What is the Motivation for Fraud?

Human nature being what it is means that there will always be some individuals who are tempted into fraudulent behaviour – for a variety of reasons. Financial motivation is often perceived as the main motivation but a desire to progress one’s career [publish or die] can also be a strong motivator. Sometimes overwork plays a significant part. If an investigator has committed to conduct many studies with inadequate resources, falsification may offer a tempting solution to the dilemma.

Conflicts of interest should not be ignored – consider the situation where a researcher has a significant direct financial or reputational investment in the success of a company’s investigational product.

Once they have succumbed to temptation, fraudsters may continue despite the risks, hoping they can extricate themselves or thinking they will not be found out. Face-saving, personal vanity, self-importance or work pressures can all play a part in continuing the deception.

How are Fraud and Misconduct Detected?

There are broadly three ways in which fraudulent data or misconduct are detected: routine monitoring activities, data trending or mining and through whistle-blower reporting.

**Monitoring**

The clinical trial monitor is on the front line when it comes to the detection of clinical fraud. If given complete access to all documents generated during a subject’s participation in a clinical study, the monitor is in a position to detect most types of fraud. Review of source data provides the opportunity to verify eligibility of trial subjects and the integrity of the data generated during the study. Cross-checking data from different sources such as the pharmacy, laboratory, radiology, etc., further enables the monitor to detect anomalies.

However, fraudsters will usually attempt to hide their activities so the monitor must be aware of ‘red flags’ that in themselves do not signify malpractice, but can be indicators that should initiate further investigation. Table 1 opposite lists a number of such ‘red flags’ and what they could possibly signify. It is important to note that all of the ‘red flags’ listed can and often do have simple explanations including ignorance of regulations and good practices, negligence or sloppiness. It is therefore important that monitors use their discretion when following up such indicators.
### Table 1: Examples of ‘Red Flags’ and Possible Implications

<table>
<thead>
<tr>
<th>RED FLAG</th>
<th>POSSIBLE IMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altersations in source data, e.g.</td>
<td>Altered or deleted data to hide</td>
</tr>
<tr>
<td>alteration in values that turn</td>
<td>inability of trial subjects, or other</td>
</tr>
<tr>
<td>an ineligible subject into an</td>
<td>non-compliance (can also indicate</td>
</tr>
<tr>
<td>eligible one</td>
<td>fabricated data for</td>
</tr>
<tr>
<td>Use of masking fluid in source data</td>
<td>trial tests not actually performed).</td>
</tr>
<tr>
<td>Obliterated or missing subject</td>
<td></td>
</tr>
<tr>
<td>identifiers, e.g. on ECG printouts, scans, laboratory reports</td>
<td></td>
</tr>
<tr>
<td>Clinic note entries not in</td>
<td>Fabricated data, e.g.</td>
</tr>
<tr>
<td>chronological order or entries</td>
<td>trial assessments not</td>
</tr>
<tr>
<td>apparently inserted between</td>
<td>actually performed,</td>
</tr>
<tr>
<td>existing entries</td>
<td>subjects not actually</td>
</tr>
<tr>
<td>Handwriting similarities between</td>
<td>treated or even</td>
</tr>
<tr>
<td>documents from different subjects, such as diaries or QOL</td>
<td>complete fabrication of</td>
</tr>
<tr>
<td>questionnaires</td>
<td>data for subjects that do not exist.</td>
</tr>
<tr>
<td>Subject diary cards of CRFs appear ‘too clean’ and without errors</td>
<td></td>
</tr>
<tr>
<td>‘Too perfect’ drug accountability records</td>
<td></td>
</tr>
<tr>
<td>Handwriting similarities between</td>
<td></td>
</tr>
<tr>
<td>Clinic note entries in</td>
<td>Trial subjects have</td>
</tr>
<tr>
<td>different subject signatures on</td>
<td>not provided their</td>
</tr>
<tr>
<td>consent forms</td>
<td>consent.</td>
</tr>
<tr>
<td>Monitoring visits frequently</td>
<td>Behaviour that leads</td>
</tr>
<tr>
<td>postponed by site staff</td>
<td>to obstruction of</td>
</tr>
<tr>
<td>Site staff frequently absent during planned monitoring visits</td>
<td>monitoring activity may</td>
</tr>
<tr>
<td>Trial documentation not available</td>
<td>indicate manipulation to</td>
</tr>
<tr>
<td>for monitoring or long delays before documents are presented</td>
<td>avoid detection of</td>
</tr>
<tr>
<td>Delays in completion of case</td>
<td>fraudulent activity.</td>
</tr>
<tr>
<td>report forms</td>
<td></td>
</tr>
<tr>
<td>Site staff are anxious, defensive</td>
<td></td>
</tr>
<tr>
<td>or complaining about monitor’s behaviour or attitude</td>
<td></td>
</tr>
<tr>
<td>Investigator is obsessed with</td>
<td>Not significant in</td>
</tr>
<tr>
<td>study payments</td>
<td>itself, but something</td>
</tr>
<tr>
<td>Unusual or unexpected data –</td>
<td>to be aware of.</td>
</tr>
<tr>
<td>often detectable without visiting the site</td>
<td></td>
</tr>
<tr>
<td>Unexpectedly low incidence of</td>
<td></td>
</tr>
<tr>
<td>screen failures, adverse events</td>
<td></td>
</tr>
<tr>
<td>Repeated values or number</td>
<td></td>
</tr>
<tr>
<td>preference in data where</td>
<td></td>
</tr>
<tr>
<td>variability is expected</td>
<td></td>
</tr>
<tr>
<td>Data submitted at unusual times, on holidays or at weekends</td>
<td></td>
</tr>
</tbody>
</table>

### Data Trending or Mining

These terms refer to the use of data generated from the clinical trial to look for unusual trends or values that may be indicative of fraud. For these techniques to be effective, the study data must be available in real time. The increasing use of electronic data capture has made their routine application possible.

Statistically valid programmes are developed that take into account the expected variability of the data and then look for anomalous data trends, typically comparing data between sites. Patterns of data such as those described in the last row of Table 1 can be quickly identified and the site exhibiting the outlying data then selected for additional monitoring or directed audit activity.

### Whistle-blowers

When a worker finds fraud or misconduct perpetrated by a colleague at the same institution and then reports it either to internal management or to an outside organisation, this is referred to as whistle-blowing. If there are inadequate controls to prevent and detect fraud within an organisation, whistle-blower activity may be the only way that it is revealed.

### Investigations and 'Directed Audits'

Once there is suspicion of possible fraudulent research activity, the next step is to conduct an investigation. After reviewing the circumstances, one common approach is to conduct a specialised audit often referred to as a ‘directed’ or ‘for cause’ audit of the individual or organisation under suspicion. The process is similar to most quality audits but there are additional techniques and considerations in the preparation, conduct and reporting of a directed audit.

### Preparation

Companies will choose their most experienced auditors to lead a directed audit as it is one of the most challenging audits to conduct and you usually only have one chance. Once a fraudster knows an investigation is under way, evidence may ‘disappear’. As well as having expert knowledge of the relevant GxPs and regulatory requirements, the auditor must know their SOPs and processes, especially concerning fraud/misconduct and the conduct of directed audits. They must also have diplomacy, tact and persuasive skills, as well as highly developed interviewing and questioning skills. Routine auditing is aimed primarily at processes but when looking at fraud cases, the integrity of the individual is under scrutiny, meaning the auditor must always have the ability to remain calm and professional under pressure.

While some companies do not consider an audit plan is appropriate for a directed audit, so as not to restrict the investigation, a formal plan may help to define the scope and potential targets for the audit. For example, in an investigation of suspected fabrication of subject diary cards, a full review of the site investigator file (SIF) and drug accountability records may not be necessary and would waste valuable time on-site. However, some of these documents may be relevant – such as signature logs from the SIP and drug dispensing records to cross-check with subject visit dates and events. If an audit plan is written, it should allow for flexibility as the investigation may take an unexpected direction.

Directed audits require as much planning as time will allow, although time may be limited as these audits often need to be conducted urgently. Auditors should ensure they have a thorough knowledge of the protocol and relevant study documents, including monitoring visit reports which will need to be reviewed with even more care than usual. Discussions with study team members are essential to ensure good insight into the situation at site as well as what is typical and atypical for the study.

Finally, it is common practice to send at least two people to a directed audit which could be either as two auditors or an auditor plus an additional person such as an experienced study monitor. This is because, if during the audit, evidence of fraud is obtained, or false statements are made, it is important to have witness corroboration by two individuals.
Audit Conduct

Directed audits usually start with a series of preliminary interviews with site staff. The objective here is to establish a baseline understanding of the research practices at the site, particularly in relation to the areas under investigation. It is important that the auditors obtain clear and unambiguous descriptions of practice and procedures of the study and record these statements accurately, as they will be referred back to later in the audit. Having two auditors present during these interviews will ensure that the questions and responses are accurately recorded.

After the opening interviews, the auditors will review the documents related to the audit scope and target. It is not possible in a short article to detail the process of investigation, as each audit will take a different path, but there are some techniques that are common to all audits. The cross-checking of records from various sources is essential and auditors may ask for records that are not requested as part of routine monitoring. For example, if there are suspicions of subject visits being fabricated, in addition to requesting the subject clinic notes, the auditors may also request appointment books, department diaries, outpatient reception records and other records to check when subjects attended for study visits.

In conducting the audits, accurate documentation of the findings of the investigation is vital. The auditors’ notes may eventually become evidence in a legal case, so every detail must be recorded. It is important to record only facts and not conjecture – for example, record what was said and not said, what documents are present, where there are conflicting facts and what information is missing.

If the auditors do find evidence of fraud, then it is common to secure this evidence by making copies of the documents – taking care to de-identify the document to protect subject confidentiality. The auditor should write on the back of the copy what the document is, where it was found and other relevant information.

Directed audits usually take more than one day to complete. Having more than one auditor present provides an opportunity to discuss with each other the progress of the audit in the evening and to plan the strategy for the next day.

If evidence is found that points towards fraud, it is important at some point during the audit to present this evidence to the suspected party. This process should not be confrontational or judgmental but taken as an opportunity for the suspected party to explain their actions. This is where the interviews conducted at the beginning of the audit have their greatest value. The auditor can refer back to these, for example “In our interview, Dr X, you stated that you did [xxx]. However, this document does not support this statement – please can you explain?”

Closing Meeting

The audit closing meeting is when the auditors present their findings. The ability to remain calm, professional and objective is vital at this stage. The auditors must communicate the facts of the investigation without criticism but openly and frankly. Even if there is clear evidence of fraud, the auditors will express this in a non-personal way. For example, rather than saying “You fraudulently entered ineligible subjects into this study” the auditor would say “I have evidence that subjects who were not eligible to enter the study had their clinical records altered to make it appear that they were eligible. These subjects were then entered into the study in violation of the protocol requirements”.

The auditors will also explain what happens next, for example, that the information from the audit will be relayed to company management or the sponsor who will decide what further action is required.

Audit Reporting

It is usual practice for a verbal report to be made immediately following the audit so that senior company management and/or the sponsor are informed as soon as possible of the initial findings. The audit report should also be written as a priority once the audit is completed. The audit report should be factual and supported by summaries or transcripts of the interviews, together with any collected evidence. Company procedures should be followed and further investigations are usually required. If later it is found that the allegations are not substantiated, or are found to be untrue, there must be a process in place to clarify company records and restore any damage done to reputations.

Communication and Reporting

Once directed audits and other investigations are completed, and a determination has been made regarding their outcome, it is essential that appropriate communication and reporting takes place in a timely fashion.

Internal Reporting

Having company SOPs to cover the detection, investigation and subsequent reporting of fraud is essential and all staff in the company should be trained on the SOPs or parts relevant to their role in the company. These procedures should include at least the following elements:

- Initial actions upon suspicion
- Escalation and communication procedures
- Confidentiality aspects
- Investigation requirements
- Evidence preservation
- Reporting responsibilities e.g. to regulatory authorities
- Whistle-blower protection

External Reporting

Many regulatory authorities require that sponsors of clinical trials promptly report to them their suspicions of fraudulent data3,9,10, and Ethics Committees/Investigational Review Boards must also be informed.

When the FDA detects regulatory violations which are so significant and/or numerous that the scope, severity or pattern of the non-compliance supports findings and are repeated or willful and involve submission of false information to the FDA and or to the sponsor in any required report, the FDA will give the highest classification of action known as Official Action Indicated (OAI). Figure 1 depicts the definition of what the FDA considers to be significant to be classified as an OAI inspection.

Figure 1: Inspection Outcomes Considered by FDA to be Designated OAI

![Figure 1: Inspection Outcomes Considered by FDA to be Designated OAI](https://example.com/figure1.png)

- Subjects under the care of the investigator would be or have been exposed to an unreasonable and significant risk of illness or injury.
- OR
- Subjects’ rights would be or have been seriously compromised.
- OR
- Data integrity or reliability is or has been compromised.
The FDA process for following up on data integrity/scientific misconduct issues is illustrated in Figure 2.

**Figure 2: Steps in FDA Investigation and Follow-up of Misconduct Issues**

**STEP 1**
- Conduct inspections to verify allegations, including the scope and extent of suspected wrongful acts.
- Collect evidence – copies of documents, documents relevant discussions and ID person with authority to correct action.

**STEP 2**
- Submit recommendations for withdrawal for each of the affected applications, detailing all specific findings and related exhibits.
- If AIP* is invoked, review the firm’s proposed audit plan for adequacy and confirm the completed independent audit information.

**STEP 3**
- Evaluate the firm’s CAPA for adequacy.
- Verify implementation and/or completion of the CAPA.

*Application Integrity Policy is a core part of the U.S. Food and Drug’s policy, focusing on the integrity of data and information in applications submitted to FDA for review.

**Prevention**

Can we prevent fraud from ever happening? Probably not, but there are a number of well-recognised actions that every organisation should take to minimise the possibilities. In a 2008 ‘Nature’ article entitled ‘Repairing Research Integrity’, Titus et al. listed six strategies to champion research integrity:

1. **Adopt zero tolerance** - all suspected misconduct must be reported and all allegations must be thoroughly and fairly investigated.
2. **Protect whistle-blowers** - careful attention must be paid to the creation and dissemination of measures to protect whistle-blowers.
3. **Clarify how to report** - establish clear policies, procedures and guidelines related to misconduct and responsible conduct.
4. **Train the mentors** - researchers must be educated to pay more attention to how they work with their junior team members.
5. **Use alternative mechanisms** - institutions need continuing mechanisms to review and evaluate the research and training environment of their institution, such as internal auditing of research records.
6. **Model ethical behaviour** - institutions successfully stop cheating when they have leaders who communicate what is acceptable behaviour, develop fair and appropriate procedures for handling misconduct cases, develop and promote ethical behaviour and provide clear deterrents that are communicated.

**Summary**

If we consider the future for managing fraud and misconduct, we need to consider the driving forces. Fraud is usually conducted by intelligent people who must realise the consequences of their actions but have a naïve belief that they will not be caught or their attempts at fraud are too smart to be detected.

By having a thorough awareness of the implications of fraud, by instituting the practices described in this article and adopting the preventive measures recommended, fraud may never be eradicated but its impact can be minimised. Ultimately, we all have a responsibility and a duty of care to the people most damaged by this practice – to the patients we all serve in our daily work.
The GCP Committee would like to evaluate if there is interest within membership to attend a seminar on Fraud and Misconduct in spring 2012. We have been conducting similar seminars periodically over the years and are now considering the development of a new updated seminar on this topic.

The seminar would be tailored to auditors working in the GCP environment in order to learn more about how to differentiate fraud and misconduct from non-compliance and how each can be managed. Topics of the seminar would include:

- An introduction to fraud, misconduct and non-compliance
- An overview of current regulations directed at fraud, misconduct and non-compliance
- A workshop exploring the differences in preparation and conduct of for-cause audits compared with routine site audits
- How reported non-compliances and suspected fraud can be effectively investigated during a site audit
- Interpersonal skills and interview techniques
- Conducting other types of directed audit e.g. investigation of critical systems failures

If you are interested, please send an email to courses@barqa.com, citing the Fraud and Misconduct seminar in the topic line of the email.

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Counterfeit Products in the Clinical Supply Chain

What is a Counterfeit Medicine?
The WHO definition of a counterfeit medicine is: ‘one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.’
The term ‘falsified medicinal product’ was recently introduced by the European Union (the EMA defines counterfeits as medicines that do not comply with intellectual-property rights or that infringe trademark law, whereas falsified medicines are defined as fake medicines that are designed to mimic real medicines). The falsified medicinal product is the subject of Directive 2011/62/EU (amending 2011/83/EC) which details measures to be taken to prevent the entry of falsified products into the legal supply chain.

Falsified medicinal product is described in Directive 2011/62/EU: ‘Any medicinal product with a false representation of:

- Its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients
- Its source, including its manufacturer, its country of origin or its marketing authorisation holder or
- Its history, including the records and documents relating to the distribution channels used.

This definition does not include unintentional quality defects and is without prejudice to infringement of intellectual property rights.’

The Extent of the Problem

The extent of the problem is not truly known as no global study has ever been performed. Being an illegal activity adds to the difficulty of truly assessing the size of the problem. However various assessments of the global magnitude of counterfeiting which do exist, (generally collected by governments in association with the pharmaceutical industry) estimate that:

- In the UK and other similarly developed countries counterfeits account for 1% of the total medicines market

- For emerging economies this is 10%, with the former Soviet republics as high as 20%

- While in Latin America, South East Asia and Sub Saharan Africa 30% of medicines are counterfeit.

The main difference being that, developed countries have well established and strong regulatory frameworks and strong enforcement agencies, compared to those of less developed countries.

The under regulated internet sales of medicines are an ever-increasing global headache for regulators; in the UK is it estimated that 50% of drugs sold online are falsified.

The classes of drugs most commonly counterfeited are genito-urinary, anti-infectives and central nervous system medicines. The MHRA has issued nine recalls since 2004 for counterfeits that reached pharmacies and patients. One of these was in a clinical trial.

Potential Impact of a Counterfeit Material Entering a Clinical Supply Chain

Counterfeit raw materials entering the manufacturing arm of the supply chain will affect the integrity of the final drug product be it the investigational medicinal product (IMP) or the comparator. These may end up with no activity or at the other extreme contain harmful substances. Trial subjects could be administered with a drug which may be ineffective or harmful. This will impact the validity of the trial data.

This can be costly to correct in terms of time, money, company reputation and even company survival. Many newly emerging biotech companies have a limited pipeline and invest heavily in one or two products being successful in clinical trials. A lot of these companies may not survive the consequences of a counterfeit finding its way into their clinical trial. The impact of having to stop trials of potentially lifesaving drugs could be considerable both to the patient and the sponsor.

How Does a Counterfeit Product Enter the Clinical Supply Chain?

There are two key routes of entry:

- The raw materials used in the manufacture of the IMP i.e. the active pharmaceutical ingredient (API) and excipients
- The comparator/or any other licensed medication used i.e. standard care, rescue medication, etc.

Raw Materials

Unless the authenticity and manufacturing conditions of materials such as the API and excipients can be assured, the resulting IMP may be rendered ineffective or harmful.

As clearly stated on both the EMA (Q&A GMP section) and the MHRA websites (Q&A on IMPs section) ‘There is no requirement for APIs used in IMPs to comply with EU GMP Part II but there remains a responsibility for IMP manufacturers to assure themselves that the API is of an appropriate quality’.

For a company willing to spend many thousands of pounds developing a drug and undergoing a clinical trial it would seem foolhardy not to invest in ensuring the authenticity of the API and API manufacturer.

‘There is no requirement for APIs used in IMPs to comply with EU GMP Part II but there remains a responsibility for IMP manufacturers to assure themselves that the API is of an appropriate quality.’

As a minimum the following should be considered:

- The acquisition of relevant documents i.e. TSE certificates, C of As, C of Cs
- Acceptance testing on receipt of the API to confirm identity, activity (if relevant) and contaminant levels
- An audit of the manufacturer. An important caveat here is to ensure sufficient focus on checking for counterfeit activities. It’s not worth simply assuming that these activities will be discovered through the normal audit process. Specific training for auditors in checking for counterfeits should be considered.

All of these requirements should be captured in a technical agreement.

The API and/or excipients may be novel and developed specifically for manufacture of an IMP. In these cases there is likely to be greater control by the sponsor and the likelihood of it being counterfeited will be low. However, if the API and excipients are well established and widely used, this makes them a more lucrative target for counterfeiters – meaning that the chance of purchasing falsified material is higher.

As recent issues with contaminated glycerol, (commonly used as an excipient) prove.

Directive 2011/62/EC includes requirements to strengthen the verification and authenticity of active substances (APIs) and extends GMP requirements to cover excipients. It also increases responsibility on the competent authority to ensure that GMP standards are adhered to and verified prior to export of the active substance.
The Comparator

Comparators are normally licensed drugs. Depending on the class of drug and quantity required, the risk of procuring a falsified comparator can be very high. The usual route of procurement is via a third party wholesale dealer as the documentation required will not usually be readily available to direct customers.

The choice of wholesale dealer is critical so it’s worth taking the time to choose one who will be reliable and has a secure supply chain. It is a given that they hold appropriate dealers licences. Other areas to check:

- Can they source directly from the manufacturer?
- Can they ensure the shipment route is completely traceable so that there is no chance of the consignment being diverted and tampered with?
- Can they procure all the drug from the same batch?
- Do they audit/perform appropriate vetting of their suppliers?
- Do they have suitable incoming checks on all deliveries?
- Do they have suitable checks on all goods prior to despatch?
- Are they abreast of regulatory requirements and actively implementing new legislation?
- Do they have a robust, mature quality management system (the best way to confirm and increase confidence is by questionnaire followed up by a physical audit)?

Good wholesale dealers will already be following the requirements laid out in Directive 2011/62/EU Article 80 which among other requirements specifies that they must maintain a quality system and keep detailed records of the products received.

Global Activities

It is apparent that there is greater global cohesion, with various groups both regulatory i.e. FDA, the EU, WHO and company consortiums such as Rx-360 working more aggressively on anti-counterfeit measures. But legislation, however significant, will never be sufficient if manufacturers are not fully committed to securing their own individual supply chains end to end.

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Spring/Summer 2011

Matilda holds a BSc in Microbiology. She has worked within QA for the past 23 years. She has held QA management positions within various companies from API contract manufacturers to IMP and virtual pharmaceutical manufacturers.

Her areas of expertise range across biopharmaceutical, dermatology and oncology products. She is currently working at Idis Ltd who work with pharmaceutical companies and healthcare providers to create access to medicines for patients with unmet medical need. Matilda is a transitional IMP QP. She has been a member of the BARQA GMP Committee since 2009.
On the face of it, scientific misconduct should not occur. Science is about the truth and so must be concerned with careful experiment and observation, and meticulous reporting of results. If there is no concern for truth, there can be no science.
What can be done?

An outstanding student had to do a schoolboy, facing my first case of fraud. At the education level. I remember, as a simple. The first line of defence starts it follows that solutions will not be completely reliable, are they?

Since this is a complicated problem, it follows that solutions will not be simple. The first line of defence starts at the education level. I remember, as a schoolboy, facing my first case of fraud. An outstanding student had to do a titration and he was colour-blind.

So I was persuaded to stand beside him and tell him what colours I saw in the titration flask. I duly did this, but when I looked at his recorded results, they were an awful lot more tidy than those I had been reporting. He was massaging the data as he went along.

Perhaps the first line of defence is to stress to all students that science is cumulative. A bogus set of results can blight an entire field of study for years. In areas like safety testing it can lead to death and suffering on a monstrous scale – look at thalidomide. So a key idea has to be built into science courses at all levels; in science, we take pride in doing the job meticulously and doing it right. If we don’t, then at some time in our lives, we might cause dreadful destruction.

A second line of defence might be some sort of policing. It is very tempting to say that all scientific results should be replicated. Someone else should repeat the experiment and see if the same results emerge. The problem with that is sheer impracticability. If we do every experiment twice, we effectively double the costs of science, which is financial suicide. However, there is a good deal to be said for some level of checking. If we submit results to journals or reports to government agencies, we are certifying that the results are correct. This being so, there can be no objection in principle to random checks on data for several years after submission. All scientists would learn to keep their data in a safe place for that long and to be able to dig it out on request.

Another strong deterrent to misconduct is the pillory. I am not talking about the old punishment, in which the miscreant’s head and hands were locked into a board, and he was then pelted with eggs and rubbish. I’m talking about the method used by the Office of Research Integrity in the United States.

They investigate allegations of fraud and then publicly state the results. They name names so by going to their website, you learn that a named researcher, of a specific university, has admitted to faking the results in four papers and as a consequence will not receive any research grant money for a period of three years. And, in case you think that is a rather light punishment, remember that the employing organisation might want to take some action as well. Indeed, they would be foolish if they didn’t. And that action is likely to involve a rather large boot.

I hope it is clear that there is no one simple answer to the problem of fraud and misconduct in science. Like any other large enterprise, science has its share of unscrupulous people and also has temptations to misconduct which can sometimes be overwhelming. Perhaps we can each do two constructive things: we can take pride in our own work and we can be alert for cases of fraud and misconduct if we see them.

The Reasons for Misconduct

Why does scientific misconduct happen? I suggest that there are three main reasons. First, there is the brutal simplicity of career pressure. If your career – and the welfare of your family – depend on your reporting successful results from an experiment, then your motives for faking results are pretty obvious: if the experiment simply won’t work, you would feel tempted to report the expected results anyway.

Second, there is passionate belief in a particular theory. Imagine that you strongly believe in a particular theory or viewpoint. You have argued for your viewpoint in conferences and publications. You do experiments to support your viewpoint. However, the experiment is a difficult one and you simply can’t get the ‘right’ results. If you admit this, you may look a complete fool. Again, the temptations are obvious.

Finally, there are commercial pressures. All businesses are expected to show a profit and, in some of them, the pressure to produce results can be agonising. Pharmaceutical companies spend hundreds of millions of dollars to put one drug on the market. If a new drug fails a single safety test, the consequences could be catastrophic – not just for profits, but for the employment of thousands of people. In those circumstances, it’s easy to see how pressure might build up within a company to fake a particular set of results. After all, experiments are never completely reliable, are they?

What can be done?

Since this is a complicated problem, it follows that solutions will not be simple. The first line of defence starts at the education level. I remember, as a schoolboy, facing my first case of fraud. An outstanding student had to do a titration and he was colour-blind.

So I was persuaded to stand beside him and tell him what colours I saw in the titration flask. I duly did this, but when I looked at his recorded results, they were an awful lot more tidy than those I had been reporting. He was massaging the data as he went along.

Perhaps the first line of defence is to stress to all students that science is cumulative. A bogus set of results can blight an entire field of study for years. In areas like safety testing it can lead to death and suffering on a monstrous scale – look at thalidomide. So a key idea has to be built into science courses at all levels; in science, we take pride in doing the job meticulously and doing it right. If we don’t, then at some time in our lives, we might cause dreadful destruction.

A second line of defence might be some sort of policing. It is very tempting to say that all scientific results should be replicated. Someone else should repeat the experiment and see if the same results emerge. The problem with that is sheer impracticability. If we do every experiment twice, we effectively double the costs of science, which is financial suicide. However, there is a good deal to be said for some level of checking. If we submit results to journals or reports to government agencies, we are certifying that the results are correct. This being so, there can be no objection in principle to random checks on data for several years after submission. All scientists would learn to keep their data in a safe place for that long and to be able to dig it out on request.

Another strong deterrent to misconduct is the pillory. I am not talking about the old punishment, in which the miscreant’s head and hands were locked into a board, and he was then pelted with eggs and rubbish. I’m talking about the method used by the Office of Research Integrity in the United States.

They investigate allegations of fraud and then publicly state the results. They name names so by going to their website, you learn that a named researcher, of a specific university, has admitted to faking the results in four papers and as a consequence will not receive any research grant money for a period of three years. And, in case you think that is a rather light punishment, remember that the employing organisation might want to take some action as well. Indeed, they would be foolish if they didn’t. And that action is likely to involve a rather large boot.

I hope it is clear that there is no one simple answer to the problem of fraud and misconduct in science. Like any other large enterprise, science has its share of unscrupulous people and also has temptations to misconduct which can sometimes be overwhelming. Perhaps we can each do two constructive things: we can take pride in our own work and we can be alert for cases of fraud and misconduct if we see them.
Dansk Kvalitetssikringsgruppe (DKG)

History
The Danish Quality Assurance Society was founded in 1986 by a small group of people from industry, CROs and the Danish Medicines Agency. This unusual support from the national agency expressed a hope to establish a common and harmonised understanding of the OECD Principles on GLP as implemented into European – and thereby Danish – national law by EU Directives.

Formation of the society was highly inspired by the UK Quality Assurance Group (QAG - now BARQA) which held an international meeting in Copenhagen a few years earlier.

Since the formation of the Federation of European Quality Assurance Society (FERQAS) in 1989 DKG has been active in the European initiatives to bring together professionals in QA. In 1996 DKG arranged a FERQAS conference in Copenhagen.

Along with the very similar QA societies in Sweden, UK, Germany, France, Netherlands, Switzerland, Spain and Italy, the Danish society has participated in numerous meetings and conferences in order to ensure and strengthen harmonisation and knowledge sharing among QA people in Europe.

DKG is now participating in the European Quality Assurance Confederation (EQAC) collaboration.

Activities in DKG
The contact with the Danish inspectorates – both for chemicals and for pharmaceuticals – has always been important and good. DKG has cooperated with the Danish authorities at important milestones, initially during foundation, during the translation process of the GLP’s to national language, during the revision of the GLP regulations 1995 – 1997, during establishment of important OECD Consensus Documents and at the OECD Event in Italy 2008.

Furthermore the Danish authorities have been active both as speakers and as participants in meetings and courses arranged by DKG.

Since 2002 the Swedish (SARQA) and Danish (DKG) QA societies have arranged a Scandinavian QA Conference every second year in Sweden or Denmark respectively. Both national and international speakers have presented current GxP topics for an audience of on average 100 participants. The next conference to be held in Copenhagen, Denmark on 18th – 19th April 2012 is now in preparation.

Active QA working groups for GLP, GCP, GMP, PV and archiving have been established – for some, many years ago – for others just recently - and meet on a regular basis to present and discuss specific issues within their field of work.

At the Annual General Meeting, invited speakers give presentations of general interest and the working groups present a summary of their activities during the past period.

The Annual General Meeting is held each March, where members of the board are elected based on the DKG Constitution, a summary of the year and information about membership is presented.

At the moment DKG has 210 members representing both public organisations and private companies.

Scope of the Society
It is the scope of DKG to strengthen QA work through contact, discussion and information. The society serves as contact between members engaged in quality assurance and serves as contact to relevant organisations.

Initially the members were engaged only in GLP and in the beginning only a few companies and QA professionals were gathered in DKG. As the number of members developed, other GxP’s – in particular GCP – became an important part of the scope for the society.

During the past years, topics from all GxP’s, pharmacovigilance and archiving have been included in the activities and in the established working groups, reflecting the interests of the growing number of members.

Contact
The DKG website www.dkgqa.dk contains information about the society and the activities (in Danish)
Education and Training

PETER DAVIES
EDUCATION AND TRAINING COMMITTEE CHAIRMAN

Since the last edition of Quasar the Education and Training Committee have met twice, at the BARQA office in Ipswich and AstraZeneca at Alderley Park. We recently reviewed our meeting schedule alongside current work plans and priorities and have decided to meet face to face on a quarterly basis with interim teleconferences to progress actions, reports and share news updates.

Distance Learning Courses
There is continued steady growth in the sales of Distance Learning Courses across all eight existing titles, with early feedback from users being very positive. Work is continuing to finalise further courses:
- Advanced Good Laboratory Practice
- An Introduction to Good Clinical Laboratory Practice
- An Introduction to Good Pharmacovigilance Practice
- Implementation of VICH Good Clinical Practice
- An Introduction to GxP Regulatory Inspections

MSc in Scientific Research and Development
With students of the first cohort now having graduated, it is an opportune time for a thorough review of the course. The Steering Group met in May and identified a number of areas for potential improvement including: module content, course structure and point of entry (including elective options alongside other related MSc courses at Cranfield) and fee payment structure. Further consultation is underway to establish the viability and value of these options for implementation in 2012.

Professional Development Courses
Demand for professional development courses continues to be strong with 2011-2012 bookings for open courses currently running slightly higher than for the same period during the previous two years. Delegate numbers for in-house courses are running at similar levels to last year.

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CPD Scheme for Auditors
Committee members are reviewing and updating the CPD assessment questions across all the GxPs as some have now been in operation for a number of years. A membership survey is planned to provide a clearer understanding of how the scheme might develop to further enhance its value and attractiveness to members and employers.
GCP Committee Members

Congratulations to Barney Horne who has recently moved jobs from PPD to Novartis (Global Head of QA Auditing) which has also resulted in a physical relocation to Switzerland. We are pleased that Barney will be staying on the GCP Committee.

Angelika Tillmann’s company, Omnicare Clinical Research is now Theorem Clinical Research and Glene Sandom has moved to Icon Clinical Research. New contact details can be found on page 48.

UK MHRA GCP Guide

The MHRA have issued a proposal regarding the production of a GCP guide. Risk adaptive trial management strategy is one topic proposed and includes the discussion of the concept of remote monitoring for low risk studies.

The current plan is for the guide to be published in 2012. It is likely that there will be limited opportunities for industry input. However, the GCP Committee is closely following the development of this guide and will look to review and comment where possible.

Consultation on the European Clinical Trials Directive has been Published

The consultation proposed several new scenarios such as a single regulatory authority assessment for clinical trials within the EU (instead of the current system of individual national authority approvals). The summary document explains the overall process and feedback. Individual responses are also available from organisations that consented to publication. BARGA submitted comments as part of the larger European Quality Assurance Confederation group.

The consultation document can be found at:

US Department of Health and Human Services Proposal to Change Rules

The US Department of Health and Human Services has proposed major changes to the conduct of clinical trials in the US. Included are proposals to have a single Institutional Review Board (IRB) approval for multi-site studies within the US, increased data security and privacy provisions and changes to the way adverse event (AE) data is collected.

There has been some criticism that the consultation period of 60 days is not sufficient and should be extended to 120 days. Further information can be found at:

Pilot EMA and FDA Joint Inspection Programme Reports

The US FDA and the EMA ran a pilot programme to conduct joint inspections and the initial phase is now complete. Both agencies have published reports on the outcome of this initiative:

UK MHRA Red Tape Challenge

As part of a larger UK government initiative to reduce the regulatory burden on industry, a consultation on different aspects of government will take place over the next few months, with the MHRA remit covered in ‘healthy living and social care’ which is planned for early 2012.
http://www.mhra.gov.uk/NewsCentre/CON126048
**Questions and Answers**

**Is a Clinical Trial Database Always Essential?**

**PREPARED BY COLIN WILSHER**

**Question:**
A relatively small Phase I clinical trial with biomarker components was audited. A database was not set up for the trial. There are paper copies of the CRFs. The principal investigator (PI) has proposed to use a spreadsheet or some other electronic format to transfer data for analysis purposes. Is this acceptable or is a clinical trial database essential? If it is not, how are requirements decided? ICH-GCP does not seem to be explicit. Please advise and provide references as applicable.

**GCP Committee Response:**
ICH GCP 2.10 requires that: ‘All clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification’.

The question hinges on what is meant by a ‘database’. A common definition of a database is ‘a system intended to organise, store and retrieve data easily’. The use of a spreadsheet would constitute a database of sorts although it would not be recognised as a standard commercial database application. Therefore, any person performing the data analysis will be using a database to access and manipulate the data. As that person appears to be the PI, he/she may be acting as both the investigator and the sponsor.

ICH GCP refers to the following as responsibilities of the sponsor (or sponsor’s agent):

1. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.
2. The sponsor should utilise appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses and to prepare the trial reports.
3. If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.
4. When using electronic trial data handling ..., the sponsor should:
   (a) Ensure and document that the electronic data processing systems conform to the sponsor’s established requirements for completeness, accuracy, reliability and consistent intended performance (i.e., validation)
   (b) Maintains SOPs for using these systems
   (c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail)
   (d) Maintain a security system that prevents unauthorised access to the data
   (e) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3)
   (f) Maintain adequate backup of the data
   (g) Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

GCP inspectors may well ask how a locked database (so that data cannot be changed) will be achieved with an excel spreadsheet. How will data entry be verified/tested? How will validation of data transfer to a statistical package for analysis be achieved? It is probably more difficult to use a spreadsheet consistently which will meet all these expectations.

Although the use of a commercially available and validated database package is not explicitly required by regulations or guidance, it does provide a platform that facilitates and documents compliance with GCP tenets.

The reader is referred to the Clinical Data Interchange Standards Consortium (CDISC), the Association for Clinical Data Management (ACDM), Good Automated Manufacturing Practice (GAMP), the International Conference on Harmonisation (ICH) Q2 - Validation of Analytical Procedures, the International Organisation for Standardisation (ISO) and the European Clinical Research Infrastructure Network’s (ECRIN) guide on data management.

http://www.ecrin.org/index.php?id=274
http://www.trialsjournal.com/content/12/1/85

**Is there a Requirement to have a Medical Monitor Available 24/7?**

**PREPARED BY KATH WILLIAMS**

**Question:**
Is there a regulatory requirement to have a sponsor medical monitor? We are a CRO and the sponsor has asked if we could be responsible for being the 24 hour medical monitor for a study. We could of course discuss eligibility, etc. with the sponsor. This is more related to providing 24 hour medical cover (which we do anyway as required for CROs).

**GCP Committee Response:**
The GCP Committee members are not aware of any explicit requirement in legislation stating that 24 hour medical cover should be in place. However, ICH E6 5.3 states that ‘the sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose’.

This ‘readily available’ statement has often been interpreted as meaning 24 hour cover. The basis for this is the argument that if there is a medical emergency involving a clinical trial subject, the treating physician may need immediate access to information about the trial, the investigational medicinal product and potentially the actual treatment given to the subject. Regulatory inspectors will certainly assess sponsor and CRO systems to ensure that continuous cover is available should such advice be needed in a medical emergency. There is also an expectation that these systems should be tested by the sponsor.

In addition, there is a general inference in US and EU legislation regarding prompt action to be taken by the sponsor in relation to safety information e.g. 21 CFR 312.32 (d) ‘the sponsor shall promptly investigate all safety information received by it’.
Good Pharmacovigilance Practice

Internal PV audits A workshop during the annual Pharmaceutical Information & Pharmacovigilance Association (PIPA) conference 2011

PIPA is the professional organisation for individuals who are involved in the provision and management of information and those involved in the fulfillment of regulatory requirements relating to drug safety.

Summary
The main scope of this workshop was the development of a robust audit programme for a pharma company called Drugs United. After a short introduction the audience was divided into four small groups. Each group had to go through four short parts of the workshop.

1. Getting ready
2. What to audit and when?
3. Planning an individual audit
4. Developing CAPAs

The first three parts of the workshop clearly reflected the view of an auditor whereas the last part covered the reaction of the audited company/department/position. The interesting split into four groups led to the development of very different audit plans, with a quite varied outcome, which reflected the varying experience delegates had with internal PV audits.

The Workshop
Ron Ward and Allison Jack were the two (extremely experienced) guides for this interactive workshop. Ron started (after a few words of introduction) with the long list of objectives to be achieved:
- Discover how audits can benefit you
- Know when to bring in the auditors
- Learn how to develop responses to audit findings
- Understand your auditor
- Learn how to develop an audit programme
- Explore how to plan for an individual audit

From this initial session, it became clear that it would be a challenge and a lot of hard work to achieve at least some of the objectives; the intention being that this would be an intense and interactive workshop. After a set of short definitions related to the ISO 9000:2005 standard for quality management (see: http://www.iso.org/iso/home.htm), the group had the chance to read a case study about a company called Drugs United.

Part one - getting ready:
The group had to find out:
- Who should be involved in the planning and delivery of the audit programme in order for it to be effective?
- What factors would make the audit programme robust?
- What would be the advantage of an audit programme?

The discussion clearly showed that the group would need some important ingredients:
- A clear commitment from management is essential to ensure the full engagement of all affected participants involved in the audit

The objective(s) of the audit must be well defined upfront and you have to monitor all actions/reactions of the people involved carefully
- A policy on sampling is helpful to collect the evidence you need
- The CAPAs in place should lead to a continuous improvement of processes
- Whenever you think about the interactions within your system you should have in mind to be as close as possible to reality

Part two - what to audit and when:
Because of the complex structure of Drugs United, it became clear that it would not be possible to audit the whole PV system in detail, in one go, but as this was the purpose of the audit, the group had to think about how to split the PV system into manageable pieces. To ensure the whole system was audited effectively the group had to consider the criteria and prioritise what was looked at. This did not sound simple and was not an easy task to accomplish!

Here the risk assessment was most important – so how were we to assess the risk?
First, the group defined who, what, when and for how long the audit would be performed for. We had to find out how the company balances the control of risk with the risk they face. Some of the major key factors involved here were:
- Product indication
- Awareness of product safety and efficacy
- Compliance with requirements
- Measurements of performance
- Complexity of the system
- Inspection history
- Time elapsed since last inspection
Part 4 - developing Corrective Action Preventive Actions (CAPAs)

The last part now reflected the necessary ‘reaction’ of the audited employees: The challenge was to:

- Choose a finding we were familiar with
- Explore what the root cause might be
- Develop a solution
- Decide how to link the solution into daily work
- Discuss what might prevent the CAPA from working

At this point it is useful to define CAPA: A CAPA is a procedure for responding to audit outcomes. It should be agreed in advance and documented. The important aim is to improve the quality management system and to get action and not promises of action.

To develop a CAPA you should follow these steps:

1. Determine the root cause of the non-conformities
2. Evaluate the need for action to ensure that the non-conformity does not reoccur
3. Determine what action is required (by whom)
4. Implement specified action
5. Record the results of the action taken
6. Review the corrective action taken

Having this clear guidance and the audit experience of the participants made this an easy part to work on.

Next, Ron presented on the PDCA-cycle for continuous improvement, consisting of four easy steps:

Plan – recognise an opportunity and plan a change

Do – test the change in a small-scale study

Check – the result and identify what you’ve learned

Action – take action based on what you learned

Finally we realised that the implementation of these steps into our daily (routine) work would lead to an autonomous improvement of the processes we have to follow every day and that it is really worth thinking about it.

Conclusion

Even though time was limited we were able to work through all these four parts. Every part (and especially the different view of the four groups) added new knowledge and insights to my understanding of a PV audit and how to develop/perform an audit in the future (I feel sorry for my colleagues – I will be implementing some actions soon). From my personal perspective, I worked a lot, learned a lot and had a lot of fun and interaction with colleagues.

CONTACT

For further information, please contact Peter Nacke, Medical Information Senior Manager, Vifor Pharma Ltd. at: peter.nacke@viforpharma.com

Peter is Global Medical Information Senior Manager at Vifor Pharma Ltd, based in Zurich, Switzerland. He has a diploma as a biologist and achieved a PhD in science in 1998. Peter joined Vifor Pharma in 2009 to establish Medical Information at HQ and to setup and implement a Medical Information System globally. In his previous roles, Peter has also been responsible for Medical Information on local and/or European level for different indications as well as additional responsibilities as Product Manager. As a biologist, with a strong scientific background in cardiovascular research, he started his pharmaceutical career as Medical Product Manager for an antihypertensive drug in 2005.
Questions and Answers from the GLP Consultative Committee Meeting, 9th May 2011

Notes from the aforementioned meeting were published in the July edition of Quasar. At that time answers to questions submitted on behalf of BARQA members were not available in a documented format. These are now available and included below.

Questions from the Scientific Archivist Group (SAG)

1. The GLPMA has recently issued guidance on retention of copies of raw data by a test facility when the original data is sent to the study sponsor. Does this replace or supplement previous advice to test facilities to retain reports and study plans indefinitely?

   The Policy document of March 2011 reflects current GLPMA thinking and as such supersedes earlier advice. However, test facilities (or test sites) should still retain details of those GLP studies or phases which were conducted; this information might be contained in historic versions of the master schedule.

2. Is there any updated guidance (since the guidance document on GLP archiving) for closing an archive? In particular can the GLPMA offer any practical advice on what can be done with general facility records, and would passing on training records to previous customers be in breach of the Data Protection Act?

   There is no updated guidance on archive closure. Such events are rare and usually need to be considered on a case by case basis - for example, is there a successor organisation that can hold non-study specific records, is it practical to send copies of relevant supporting records to study sponsors, etc.

   We cannot provide definitive comment on the application of the Data Protection Act, but any 'Personal' information such as a CV that contains personal information is likely to be covered.

3. What are GLPMA expectations of companies contracting out archiving of GLP electronic raw data?

   The section of the booklet 'GLP Guidance on Archiving' that refers to the use of a contract archive will apply equally to a contract electronic archive service, but there may be additional technical issues that would need to be considered.

4. The guidance on retention of copies of raw data states that the interval between inspections does not exceed 27 months. Is this a definite commitment that test facilities can rely on when planning for future inspections?

   The booklet 'GLP Guidance on Archiving' refers to GLP inspections at 24-27 month intervals, but does indicate that data should be retained for one inspection cycle - effectively 2-3 years. However, the risk based GLP inspection programme is continuing to evolve and there is the possibility that facilities with a low risk profile and a good compliance history may see some relaxation of inspection frequency in the future. These facilities would therefore need to extend the period for which they would retain copies of study data.
Questions from BARQA

1. This question is relating to the revised UK GLPMA guidance document entitled ‘Guidance on the use of non-GLP compliant facilities for the conduct of study phases and notes on the intention not to claim GLP compliance for parts of regulatory studies’ (Oct 2010).

The guidance specifies that the MHRA should be notified, not only when a non-GLP test site is to be used to perform a phase of the study, but when a GLP test site is performing a phase non-GLP.

However,

Page 1 of the guidance document under ‘Intention not to claim GLP compliance for part of a regulatory study’ 2nd paragraph states ‘the GLPMA has a statutory duty to ensure that regulatory studies performed in the United Kingdom are conducted in compliance with GLP. Consequently, they should be notified whenever there is an intention not to claim GLP compliance for any part of a regulatory study. This will include any work that will be undertaken within a GLP compliant facility for which there is no intention to claim compliance’.

Therefore should the MHRA also be informed if a GLP study includes an element for which there is no intention to make a claim of GLP compliance, when the study is conducted at a single site? This situation may occur if a sponsor has requested some additional analysis for information only (for scientific/additional information it is sometimes beneficial for the sponsor to make full use of the samples/tissues generated on a study even if no GLP compliance claim can be made for the specific phase; this could preclude the need for a separate non-GLP study).

In addition, it could be perceived that the guidance puts the UK at a commercial disadvantage in comparison to some other countries. Such countries might not have documented guidance in place, but providing the study director (SD) is transparent in their Compliance Statement, are comfortable in the receiving authorities accepting or rejecting data associated with a GLP disclaimer. Please comment.

Please refer to the minutes for information relating to this question.

Generally speaking, if analysis is performed that does not form part of the main GLP study because the information generated is for research purposes rather than to assess safety, the GLPMA would allow the work to be performed in a non-GLP environment. The GLPMA would expect the SD’s statement to clearly identify the non-GLP work and explain why a claim of GLP compliance was deemed necessary.

2. In the UK is it acceptable for a SD to declare a study compliant with GLP if there are isolated exceptions of non-compliance which are potentially major in nature (i.e. could invalidate the results)?

Specifically, test item and test item formulation characterisation missing or incomplete because the analytical methodology hasn’t been set up for various reasons (e.g. precocity of study conduct in the development process, technical difficulties due to interfering excipient in formulation). There is, in France, a current of interpretation by the agency which reasons that potentially invalidating non-compliance should preclude declaring the study conduct to be GLP compliant even if the non-compliant elements are detailed and discussed as exceptions in the compliance statement.

Any non-compliance that could invalidate the results of a GLP study would prevent the SD from making a claim of compliance.

If a discrete part of a GLP study is deemed not to be compliant then there is a possibility that the SD can still make a partial claim of compliance, but this would have to be determined on a case by case basis.

3. A GLP inspector stated that only significant deviations from the principles of GLP need to be noted in the SD’s statement of compliance. With regards to the information requirements on sample identification and characterisation, contained within the GLP Regulations, what would constitute a significant deviation? An explicit answer would be extremely useful as this issue is problematic when limited information is available.

We have been criticised for having insufficient information in some studies but cannot find guidance anywhere - clearly we were judged against some criteria; it would be useful to know what these are!

Case example:

One of our clients has a number of samples with us for testing, where we don’t know much about them. We have generic material safety data sheets (MSDSs) which don’t give much idea of the chemical composition, no batch number, purity, expiry date or homogeneity. The client is testing the products of a different company as it may use them in the manufacture of its own products. We have requested this information and been told that it isn’t available, and the composition is proprietary. The names are all trademark type rather than chemical names.

A significant deviation is generally something which impacts on the compliance of the study or the ability of an assessor to interpret the results of the study.

If the SD has no information on the nature of the test item they should make this clear in their statement of compliance.
4. Questions relating to test item quality and level of characterisation.
- There is often a wish to use GMP level characterisation. Can you comment on what that means, e.g. GMP certified batches according to memorandum of understandings?
- What level of certification should the involved GMP laboratories have - certificate from the national GMP inspectorate?
- Is it acceptable that there is no formal quality system for characterisation of the test item in a toxicological study?

There is no requirement to perform test item characterisation in a GMP or GLP laboratory. However, best practice would be to perform the characterisation of test item in a laboratory which had a recognised quality system. In contrast there is an expectation that the homogeneity, concentration and stability of test item in vehicle are performed in a GLP laboratory. However, in some circumstances it may be more appropriate to perform this type of work in a GMP laboratory. This must be decided on a case by case basis.

If GMP laboratories are used to perform formulation analysis the test facility should check to ensure they have been inspected by a national monitoring authority.

5. During a GLP inspection by the Danish Medicines Agency last year, the following topic was discussed:
Company 1 had sold products to Company 2. All data had been transferred to Company 2. It was the inspectors’ expectation that Company 1 at least should keep copies of the GLP studies in order for the studies to be available for inspections at the Company 1 facilities, but they would follow up with other Agencies. The conclusion was never provided to Company 1, where copies of the GLP studies are now on file. What is the UK GLPMA’s take on this?

(Following issue of the UK GLPMA retention document (March 2011), what is the UK GLPMA expectation when an asset (test item) is sold to another company; in this case all raw data/ records of associated studies will be passed over to the buyer).

The UK GLPMA expects GLP facilities to keep study data or a verified copy of study data for one inspection cycle. There is no expectation that study data is kept indefinitely by contract research organisations and in many cases it will be returned to the sponsor.

6. The authorities in Thailand have been asking for letters of certification to support submission of studies to their regulatory authorities, this is causing a huge amount of work that is considered by many to be unnecessary now that Thailand is a provisional adherent to the OECD MAD agreement. In line with the OECD MAD agreement the Thai authorities should now be obliged to accept reports coming out of UK test facilities without the need for these letters, has any progress been made in addressing this issue?

Andrew Gray met with the Thai representatives during the April OECD meeting. The Thai representatives indicated that they would get in touch with the relevant ministries and explain to them that these requests should stop.

7. Has any progress been made regarding guidance relating to pathology and pathology peer review? What is the current status?

The document has gone through an initial round of consultation with stakeholders. The consultation raised a large number of questions. A second version of the document is currently being drafted and will be discussed at the next OECD GLP working group. A further round of consultation is likely to be need before the document can be published.

8. This question is relating to Incurred Sample Reanalysis (ISR) and what is acceptable in terms of management and reporting of the work:
- Work set up as a separate study (with study plan and final report)
- Work set up as additional validation (amendment to validation study)
- Work conducted and reported as part of the study where samples have been originally analysed?

Any of the above would be acceptable.
Good Manufacturing Practice

ALAN PIPE
GOOD MANUFACTURING PRACTICE COMMITTEE

Since the last issue of Quasar the Committee has been busy preparing for the Annual Conference. Although there was no GMP QA Clinic at the Conference this year there were representatives of the Committee there and we are always very keen to hear from the BARQA GMP membership. Here are some updates you may be interested in.

Questions and Answers

Question:
A product is to be manufactured under a manufacturer’s/importer’s licence (MIA) (IMP) in the UK, for export to the US for a clinical trial. This product will be certified by the UK QP (IMP). The active pharmaceutical ingredient (API), manufactured in the EU, is commercial material and has a drug master file. Is it necessary to audit the API manufacturer in order to certify the clinical product, especially as QP certification is not required in the US?

Answer:
No - we do not believe there is a requirement to audit.

Question:
We are a CRO and have a study coming up which includes the use of a marketed product but it is a double blind placebo controlled study. The sponsor has confirmation from the MHRA that they are not required to submit a clinical trials application (CTA) for this study as it does not meet the definition of an IMP. We have requested to look at what they sent to the MHRA (currently pending this from the sponsor).

Answer:
Depending on the nature of the study it is possible for it to be defined as not being a clinical trial - irrespective of the products being used. It is not automatic that use of a placebo means a CTA must be submitted.

Qualified Persons (QPs) please take note!
The EMA Reflection Paper on use of interactive voice response (IVR) technology to justify not including reanalysis/expiry dating on the label for clinical supplies is proposing yet another task for the QP. Please see the link below; the last date for comments is 15th February 2012.


For Those Involved in Advanced Therapy Medicinal Products (ATMPs):
A reminder that EMA has issued a Committee for Medicinal Products for Human Use (CHMP)/Committee for Advanced Therapies (CAT) position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products, effective June 2011. See link below.


Also note the forthcoming workshop on ATMP’s CAT-European Society of Gene and Cell Therapy (ESSCT) Satellite Workshop ATMP: from promise to reality – 27th October 2011, ESCG annual meeting, Brighton (UK):


BARQA GMP Discussion Forum:
Please remember this is open for all relevant questions from the membership and the Committee will respond with the best advice we have. A couple of examples of Q&A’s that can be accessed via the website follow.

I always understood that if a marketed product was in anyway modified from its marketing authorisation, then it is an IMP. For example if the IMP is repackaged or relabelled. If this study is a placebo controlled double blind study then the IMP must be modified from its marketing authorisation.

Can anyone give me any advice?
There was no update in the July issue of Quasar – my apologies for that. Since the April edition of Quasar, the Committee have met once face-to-face at Stansted airport and have held two telephone conference calls.

It is with regret that the Committee accepted the resignation of Dana Winstanley. Due to a change in her role and associated re-location, Dana felt that she could no longer continue with the Committee. Dana had been on the Committee for a number of years and her valuable contributions will be missed.

However, we have welcomed a new addition to the Committee in the form of Tracy Duggan, who works for Pfizer Animal Health, based in Belgium. We look forward to working with Tracy in the future.

The collaboration with the Animal Health Speciality Section of the Society of Quality Assurance (SQA) resulted in a joint presentation at the SQA conference in San Antonio in March 2011. The 90 minute session was presented by Larry Thomas and Marci Murphy of SQA and Sven Buckingham of BARQA. Fortunately the feedback was very positive, since Larry and Sven will be presenting a pared down version at the BARQA Annual conference in Bristol.

The production of the joint articles (on global vaccine development, multi-site GCP studies and multi-site GLP studies) by the Committee and SQA has stalled somewhat. However, a recent push should lead to the publication of an article on global vaccine development at the end of the year.

The Animal Health sessions at the recent SQA conference benefited from the attendance of four FDA inspectors and one from USDA. One interesting outcome from the FDA presentations and the subsequent discussion was the lack of quality in the dossiers that are submitted to the FDA reviewers. This did rather beg the question as to whether or not QA should audit dossiers. This is a topic for future consideration and discussion, perhaps?

The Committee are in the process of compiling a membership survey, aimed at focussing our efforts to meet the needs of those BARQA members who are involved in the animal health industry. As and when you receive this survey, please do take the time to complete it – we cannot do our job properly without your input.
Our intention is to keep the BARQA membership informed of regulations concerning computing and of topical issues on computing which can influence how compliance with these regulations is best achieved. The Committee, in conjunction with the BARQA office, run two professional development courses on how to audit and on how to validate computerised systems. You should consider attending these courses if you audit computerised systems or you are involved in validating and administrating computerised systems. We have also run various seminars on topical computing issues. We are working on various projects and are preparing a number of papers to be published in future issues of Quasar. We are also eagerly monitoring the BARQA web discussion forum for member’s questions on computing issues. The Committee endeavour to respond to your questions promptly. You can discuss issues of computing and compliance with us through the forum or by contacting any one of us.

The Committee haven’t met since our last meeting in June. After enjoying summer holidays, relaxing in the sun in exotic locations, there has been a flurry of activity to ensure that the presentations in the computing sessions at the annual conference were no less than ‘the best ever’. We included a number of interesting and topical presentations on computing issues and ran a challenging workshop on electronic records and electronic signatures.
Quality Systems Workbook

Quality Systems Workbook

A major initiative for the Outreach Working Party was the production of a Quality Systems Workbook which has now been completed and was launched at the BARQA Annual Conference in Bristol. The following gives a flavour of what the Workbook is about, but what is key is that this is a starting place or refresher aid, and is aimed at the Outreach target audience, not those who are already fully embroiled in or au fait with regulatory quality systems.

What is a Quality System?

A Quality System sets out the standards that you are working to and how you are going to meet them. The system should define what people, actions and documents are going to be employed in order to carry out the work in a consistent manner, leaving evidence of what has happened. It may include manuals, handbooks, procedures, policies, records and templates. The terminology used by individual organisations is less important than the purpose and use of documents and it should be realised that the fundamentals of a Quality System are the same regardless of what the work is. The same principles can be applied whether you are an academic research laboratory, a medical device manufacturer or a hospital clinical trials unit.

What is the aim of a Quality System?

A Quality System aims to ensure reproducibility and reconstructability, and compliance with whatever standards you have set. This is the essence of good science. A good Quality System ensures the documentation of a testable hypothesis, agrees resources to test the hypothesis in a reproducible manner, ensures that the testing is carried out by competent people with minimal risk of falsification or accusation of falsification of data and ensures that, whatever form the reporting of that data takes, it reflects the evidence generated during the testing.

Quality Systems Workbook

Understanding, interpreting and implementing a Quality System is a skill in its own right. The aim of this new Workbook is to provide tools and a practical approach to develop a Quality System that works for the user. The Workbook concentrates on the core, underlying principles of quality which are pivotal – explicitly or implicitly – to all quality management standards that impact on research and development.

These principles are also fundamental to the conduct of efficient, reliable and credible scientific and clinical work and will help the user to design and implement a practical Quality System that works for their organisation to make it more productive and compliant.

The Workbook may also help users in the task of persuading others of the importance of such a system. It is aimed at the doers within the Outreach target audience who will either have been delegated the task or are volunteers who have seen the need for a Quality System.

The Workbook is available to both members and non-members as a free download on the BARQA website homepage at www.barqa.com. As part of the Outreach Working Party remit the easy accessibility of this document was felt to be critical to its implementation by the target audience. It is envisaged that from the starting point provided in the Workbook, users will become more familiar with the concepts of working in quality environments and will discover the usefulness of accessing more of BARQA’s services and products.

Without the commitment, perseverance and input from members of the Outreach Working Party this Workbook would not have been created. It was critical for the scope of this publication that suitable individuals and organisations were involved in both the writing and in the review process and thanks go to them for the significant effort and time given to this work.

LOUISE HANDY OUTREACH WORKING PARTY

We would greatly appreciate any feedback on the Workbook and its content. Please forward this to: tward@barqa.com or outreachworkingparty@barqa.com
Mystery Tour to Roadmap

In 2006 a number of issues with the regulation of pharmaceutical development became very obvious and very personal. I was brought in to set up a new facility in London, which would do things that weren’t around when most of the legislation was created and certainly wasn’t at the forefront of the minds of the European Commission when they developed the rules and guidance documents.

What I needed was a way to gather all the potentially pertinent requirements into some sort of order and check them against what we proposed to do. From there, I could establish what requirements we could and could not meet and, after assessing the risk, develop a plan to mitigate the risk or try to explain myself when faced with the MHRA.

Now, most large pharmaceutical companies have two things which are supposed to help with this sort of thing, a development plan and a quality management system. Unfortunately, the development plan, which shows all the stages for getting your product to market, usually focuses on the needs of doctors and scientists rather than quality professionals. It normally doesn’t include links to the current legislation and guidance governing a particular process.

The quality management system is supposed to include those links, however it’s designed to cover activities that already happen in an organisation, usually focuses on the needs of doctors and scientists rather than quality professionals. It normally doesn’t include links to the current legislation and guidance governing a particular process.

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We know that not all of BARQA’s members are involved in pharmaceutical development in Europe, so we are looking to expand the remit of the Roadmap(s).

If you have experience in the development process and regulation of the following areas, then we want to hear from you:

- Medical Devices
- Animal Health
- Pharmaceutical development outside the EU
  - FDA
  - Japan
  - Rest of the World

If you want to see a roadmap for your area of interest, then we need you to get in touch, if you don’t, it won’t happen.

Finally, if my cajoling on the basis of helping others and yourself hasn’t worked, in these days of economic woe, it can’t be a bad thing to have membership of a professional body committee on your CV.

As a member of BARQA I naturally, thought that I’d have a quick scan of the website and voila, as they say, all my problems would be solved... well, five years later we have that in the Regulatory Roadmap and it will shortly be accessible to everyone.

Along the road, from the initial disappointment and realisation of the work ahead, came the added realisation that I was lucky. I had a large organisation behind me, a supportive professional body and sufficient control of my activities to get the job done. This lead to the proposal that BARQA should develop a roadmap to help those who didn’t have these advantages and help our profession get a better understanding of the needs of our colleagues, who work in a different part of the development process.

With the help and dedication of a team of volunteers, the first stage of the Roadmap is now imminent. We have a description of the pharmaceutical development process, in Europe, with the most relevant pieces of legislation linked in directly. In addition we have given members the ability to access help and advice from the same source.

We don’t claim to have created a panacea to solve all your problems and answer all your questions, after all, this is a living document, with regulations being constantly updated and no guarantees that what you’ll find in those links is internally consistent; however it should give you a flying start.

There are a number of ways you can help. The group who created the Regulatory Roadmap are experts, but not omniscient. If you see something we’ve got wrong or missed out, please get in touch, so we can improve the system for everyone.

Please contact me, Roy Baxendale rbaxendale@barqa.com or email the BARQA office:
editor@barqa.com with ‘Roadmap Phase 2’ in the title

ROY BAXENDALE
REGULATORY ROADMAP WORKING PARTY
Clinical Evidence to Support the Development of Medical Devices

The first Medical Devices Working Party one-day seminar was held at the Radisson Blu Hotel, Stansted Airport, on Wednesday 13th July.

Rikke Arendt Christiansen (Qmed Consulting) described the regulatory requirements for medical device development as enshrined in the ‘New Approach’ EC Medical Device Directives. Device classification is based on risk. Oversight of the manufacture and CE Mark holder is by Notified Bodies, regulated by their respective EU Competent Authorities. The Directives are supported by standards relating to clinical documentation (MEDDEV’s) and cover more than 70,000 different types of devices marketed. To demonstrate safety and performance of a device requires clinical data, which may be gathered by either conducting a clinical investigation on the device or a clinical literature review of studies of a similar device or clinical experience reports of the device or a similar device. For the similar device, equivalence needs to be demonstrated. The Directives rate safety of the device to patients, users and others as paramount, with the elimination or reduction of risk rated against patient benefit. Devices are designed and packaged for their intended use, although the potential for misuse should be considered. Potential side-effects of the use also need to be considered. Clinical evaluation consists of a comparative review of the performance of the device in use and reported side effects to assess the acceptability of the benefit/risk ratio. This must be a critical evaluation. There is no requirement to do a specific clinical study. Part of the clinical evaluation should be a gap analysis. This may identify the need for a clinical study of the device, especially if it is novel or uses new materials in its manufacture. The clinical evaluation process aims to demonstrate conformity, identify and evaluate data in respect of safety and performance, and generate missing data. This is crucial to demonstrate how claims about the device are defined and justified, risks are assessed, the device design, especially materials equivalence and biocompatibility, and the definition of users/patients. Identified data must be documented and reported with good statistical power. While double blind trials of devices may be rare; anecdotal evidence is not acceptable.

John Andrews (LRQA) focused on clinical evaluation of a device by the literature route. Medical Device Directive Annex 10 and supporting clinical guidelines were reviewed from a Notified Body perspective. CE Mark holders declare compliance of their devices to the requirements of the Medical Device Directive 93/42/EEC, as amended 2007/47/EC. Clinical evaluation may be regarded as design validation in order to verify claims made for the CE marked device to reflect the user/patient expectations of the device. Manufacturers demonstrate conformity by the quality system route using controlled defined processes which are systematic and reproducible. Notified Bodies challenge these processes, according to device risk. Critical evaluation of relevant scientific literature should relate to safety, performance, design characteristics and intended purpose of the device, where there is demonstration of equivalence or the data demonstrate compliance adequately. Data, of known provenance relevant to the standards, and the device, either the same device or equivalent, is appraised and analysed. Conclusions drawn should ascertain if the data are sufficient to declare conformity. Missing data may need to be generated by carrying out a specific clinical investigation [see MEDDEV 2.7.1 3rd December 2009].

Patricia Aherne (Premier Research) outlined the process of updating design risk analysis based on clinical data output and complaints reviewed against clinical evaluation requirements. Risk management tools were reviewed as a systematic application of quality management system processes to the assessing, controlling, communicating and identifying hazards and their consequences (ICH Q9 (2008); ISO/IEC Guide 73: 2002; ISO14971:2007; US 21 CFR 820).
Standardisation facilitated risk management, as a planned, communicated and transparent process. The evaluation of risk to quality should be based on scientific knowledge linked to patient protection, with effort, formality and documentation commensurate with the level of risk.

Erdmann Zippel (D-Target, Premier Research) gave an overview of how to perform a medical device clinical trial from an operational viewpoint. Trials may be conducted to assess feasibility or prove concept, declare conformity, for post market surveillance, for marketing or for scientific data collection. In all cases it is to meet a regulatory need in accordance with ISO14155. Items to consider during trial set-up include:

- Design of case report forms for collecting data required
- Insurance, which is mandatory for intervention studies
- Mechanisms for device accountability at site
- User technical feedback or complaint reporting
- Site selection needs to ensure that the experience, resources and patient population is appropriate to the study proposed. The site needs to have adequate equipment, suitably trained staff and an investigator with appropriate experience. Potential conflicts of interest must be declared. The site should have adequate dedicated storage for the devices. The study requires approval from an Ethics Committee and Competent Authority. These may progress in parallel, but the Competent Authority will not approve the study without a positive ethics opinion. Additional approvals may be required if, for example, radiation exposure occurs. The clinical study proceeds in phases, thus:
  - Initiation
  - Enrolment/baseline
  - Monitoring
  - Discharge
  - Follow-up to assess outcomes

Safety reporting throughout the study to the Competent Authorities and Ethics Committees is mandatory according to prescribed time limits. For post marketing trials only serious adverse device effects considered to be related to the procedure or device need to be reported. However for clinical evaluations all device safety are crucial irrespective of cause. Device deficiencies need to be reported (MEDDEV 2-12-1 and 2). Annual safety updates should be compiled, reviewed and reported. Issues impacting on the progress of a clinical evaluation may include:

- Low patient enrolment
- Device technical issues
- Site non-compliance
- Inconsistent or incomplete data
- Under-reporting of adverse events
- Improper device handling
- Incomplete follow-up
- Non-compliant patients
- Lack of investigator time

Patricia Aherne then outlined study considerations from a regulatory QA viewpoint. As more devices are used in treatment, there has been an increase in serious adverse event reports. Between January and June 2011 the FDA issued 37 warning letters. ISO14155:2003 saw the start of a harmonisation process which continued with updates in 2009 and 2011, which should lead to the mutual acceptance of data. ISO14155 and GCP may be interchangeable in respect of patient safety and patients’ rights irrespective of whether an investigation product or medical device is being tested. Terminology differences do exist, i.e. safety reporting for devices and pharmacovigilance for pharmaceuticals; but some terminology can be generic, i.e. investigational product would cover IMP and device.

Procedures can be easily harmonised to cover both devices and pharmaceuticals, as perceived differences are more often due to semantics. The main QA challenges in device trials are:

- Lack of investigator training
- Lack of processes or procedures
- Poor storage and accountability issues
- Lack of documented training of support staff

Erdmann Zippel introduced the workshop sessions by inviting four groups of delegates to individually address a set of questions covering issues raised during a orthopaedic trial of a disc replacement device (Class Iib) when first used in man. The workshop provoked interactive discussion of the issues in setting up and managing the trial, which enabled delegates to apply the principles presented earlier into a practical context. These discussions continued during the Q&A which was appreciated judging by the active participation and questions.

ALAN DENCH
MEDICAL DEVICES WORKING PARTY
The Auditor’s World, 9th June 2011
The Anglia Regional Forum filled the room at the British Racing School with the 66 out of the 71 delegates who booked, including the 7 speakers, attending the “The Auditor’s World” – a broad combination of talks to get everyone up to date and learning from the experience of others.

More Effective Auditing
After everyone had registered, Andrew Hersom started the session with his summary talk on the art of effective auditing in the GxP field. Andrew’s 31 plus years in the Pharma industry gave rise to several useful tips on how to get the most out of an investigator site audit and not ‘generating crates of paper’ (GCP!). Preparation and getting to the bottom line about the purpose of a study and its intended product were keys to success, quickly followed by listening carefully to the answers given. Checking out the evidence and not just seeing that it was there and thoroughly identifying the definitions and procedures used, were also recommended as good practice. Andrew also favours early audits because they yield the most productive quality assurance for a study - picking potential and actual issues/reassurance early. He finished by reminding everyone of the need to make the study/computer system requirements testable and fit for purpose.

From Bits and Bytes to Benchtop and Clinics - Risk-Based Computer System Validation (CSV)
Next it was Trev Simmons’ turn to turn the complicated world of CSV into bite-sized chunks. He neatly reassured all those present that it really only boiled down to just four easy steps: a QA system, a GxP risk/critical assessment as per the QA system, the intended purpose documented as per the QA system and the evidence that the system performs to the intended purpose as per the QA system and in accordance with the risk assessment. Easy! He then soothed the quizzical brows by relating 21 CFR part 11 nicely with Annex 11 before pointing out that it was all about the data, how it was secured, the risk level to the IT system, the patient and the science, and how the data was made available, comparing frying an egg in a saucepan with frying it in a frying pan - both do the trick but one is just easier to serve from than the other. He finished by reminding everyone of the need to make the study/computer system requirements testable and fit for purpose.

GCP Hot Topics
After a brief network break, Jon Read from Gilead took the stand for this, his first, presentation for the Anglia region and neatly summarised the multitude of changes occurring in the field of GCP. eCRFs and data entry are causing the EMA and FDA to deliver their guidance on the modes, flow, and management of data from CRFs as well as what will be expected during inspections. The importance of going back to the true source is being stressed especially in relation to subject’s medical histories and diagnoses. Jon raised the thorny issue of privacy of data when patient’s electronic records need to be viewed when they are on a database containing non-subject’s records. He then moved onto the new guidance relating to clinical laboratories released by the MHRA, EMA and BARQA over the last two years before moving onto the EU Clinical Trials Directive which is due to be revised in 2012 to ensure better harmonisation, define insurance requirements for subjects, sponsor responsibilities and guidance on the issue of informed consent from subjects when they are not in a fit state to give it. Jon also brought everyone up to date on the European Clinical Trials Registry which is now publicly available. He embarked on a whistle stop tour of an auditor’s world by touching on the UK, US, Turkish, Argentinian, Chinese, Indian and Russian GCP updates before finishing on the problem surrounding the Russian requirements for subjects’ insurance.
GLP Update

Jane Wright from Battelle UK Ltd presented the GLP Committee’s summation of all things GLP. She started with international updates on those countries who have now achieved full adherence to the OECD MAD and those who have not. The OECD news that peer review on Guidance on Pathology may or may not be drafted, following the large volume of comments, was greeted by those working in the GLP field, with a mixture of despondence and humour. The FDA seem to be taking things a little more positively - Jane reported that they are seeking comments on whether GLP regulations should be amended in nine key areas, especially in relation to falsification of data. The GLPMA have issued guidance on out of specification results, which is reportedly aligned with the existing FDA guidance. Alan finished by describing the changes to FDA guidance on process validation which came out in January of this year and the EU Pharma Package review.

A delicious lunch was interspersed with the sound of delegates comparing wisdom on the GxP questions for the bingo quiz. The first three completed ‘bingo’ cards with the correct answers on, received incremental sized bottles of champagne to reward their efforts. Those lucky to receive these prizes for their intellectual prowess were: 1. Jon Read 2. Tania Young, Tracey Sindle, Tim Stiles and Trev Simmons 3. Richard Pennicard, Ian Davey and Sarah Fryer

During the lunch break, the BARQA presentation was also available in the presentation theatre for all those wishing to see what BARQA is about, and further networking opportunities were available outside in the warmth of the racing school grounds.

Auditing in the Far East

Cathy Midgley gave us a very amusing and anecdotal talk on the specificities of Far East auditing. The challenges of adequate preparation far outweighed the usual 4Ps! Cathy reported on the need of the QA auditor to carefully prepare their conduct, travel arrangements, availability of local currency as well as methods of greeting and gift receipts. She also alluded to the differences in source record keeping as well as consent taking which can take the uninitiated by surprise if not forewarned! She finished by advising auditors to review the Western approach to business versus the Eastern philosophy of the importance of ‘team’.

The Archiving Process - What Lies Beneath!

Tim Stiles, the Director of Qualogy - who provide a regulatory contract archive service and specialise in QA consultancy as well as contract archiving, dug into the requirements for suitable archiving including the placing of the Investigator Site File (ISF). In this culture of ‘trust but verify’, Tim described the need for ISF’s to be kept carefully with the contents clearly defined as well as readable. With data being kept for indefinite periods, this can be more complex than it seems but entirely necessary to establish trust in the data and prevent the risk of fraud by the sponsor. Tim also guided CRG’s to equip themselves with lasting knowledge of where the ISF’s and study data is archived so that it outlives any change in company staff. He also described the role of the archivist and their position within the company, no doubt drawing on his years of experience in the archiving and QA field. He also touched on the responsibilities of the study director and the principal investigator in this country and abroad on accepting and maintaining the trail of accountability for the study data amongst other things, noting the differences in the level of detail required by OECD countries. He finished by describing the importance of restricting the data that can be retrieved again to prevent the risk of fraud and maintain the integrity of the study.

The day concluded in a timely and effective manner with a promise of another Anglia forum in June 2012 – exact date to be confirmed. The organising group was very grateful for all the help received from the staff in the BARQA office, especially Danielle and for the staff at the British Racing School for the arrangements.
A total of 37, including presenters, participated in this Regional Forum – a record – previous attendance was 33 in 2010 and 22 in 2009. Members accounted for 27 delegates, just over half the ANZ membership and many travelling from interstate or New Zealand.

Dragana Milic from the Office of Manufacturing Quality of the Therapeutic Goods Administration delivered an Emerging Issues Brief. Within this topic Dragana spoke on Quality Product Review, Quality Risk Management (QRM) and the Validation of Computerised Systems in Clinical Trials. Two areas were identified as frequently deficient:

1. Risk Assessments: Must be performed (and documented) on:
   - Critical Processes
   - Critical Parameters
   and include change control, trend monitoring of both non-conformances and within specification data – feedback mechanisms to improve processes are often missing.

2. Computer Systems: Critical parameters are:
   - Data Integrity
   - Data Security
   Validation:
   - Site responsible for user requirements specification
   - Supplier can be responsible for installation and test protocols
   - Operational and performance qualification can be contracted but should be independent of the supplier
   - External access should be considered, for example that inputs from authorised clients are received in the correct format
   - Physical security should be addressed, e.g. theft of computer hardware

Network qualification is commonly omitted from validations. There should be network specific tests including:
- System access (e.g. network penetration testing)
- Load testing (low and high user levels)

The audience raised the issue of IT validation in facilities designed for community healthcare but in which research is conducted. It was noted that there are wide differences in the quality of IT systems in different hospitals – IT systems may be entirely suitable or inadequate for use in clinical trials. If problems are found, TGA may raise these with state regulators.

Nick Giglio of Roche presented the Roche in-house system for Competency Training for GxP Auditors. He discussed his interpretation of competency being ‘a demonstrated ability to apply knowledge and/or skills and where relevant, demonstrated personal attributes’. Using ISO/IEC 17024 and 19011, Roche auditors developed a system description for auditing auditors, including development of both auditing and technical competencies and the evidence guides for verifying those competencies. Development of training materials was accompanied by the evolution of witness auditors. Biennial auditor meetings were implemented to cross fertilise and share experiences, and to develop the system to link to global changes to the pharmaceutical regulatory landscape.

Louise Calder and, briefly, Jenny Pyke spoke on the topic GLP’s in Australia. Louise spoke of the history and requirements of GLP, the agreements for mutual acceptance of data and a clarification of the difference between OECD GLP (for pre-clinical studies for regulatory submission) and the GLP principles that are the basis of other standards for laboratories (e.g. ISO/IEC 17025 and for medical laboratories ISO 15189). Jenny spoke on a new accreditation process for pure R&D laboratories based on ISO 17025. The costs associated with accreditation may be relevant to the federal government’s R&D tax credits initiative.

Louise described international OECD GLP issues such as the 25th meeting of the OECD Working Group (April 2011), revision of CFR part 58, annual overview, non-compliant studies and facilities; domestic issues such as a breakdown of the 24 Australian GLP registered facilities, Australia’s on-site evaluation in September 2012, reminder that NATA’s GLP programme only covers Australian facilities, NATA only inspects overseas facilities at the regulator’s request.

Jonathan Taylor of Roche presented the topic Quality Risk Management Applied to GCP, GLP and PV. All the aspects of QRM were discussed, e.g. why report adverse events (AEs); what happens if AE’s are not reported; what are the consequences to the company if AE’s are not reported; how does QA prevent some AE’s from occurring; data collection and the role of auditors in the discovery of risk. QRM requires an audit programme that will reflect where the risk really lays. All audit reports must be analysed to ensure QRM signals are meaningful and the system learns continuously, and that QRM signals are appropriately addressed by the company owners. Jonathan concluded that a risk management approach must be a well structured process that will see problems coming, assess which are really going to hurt and be able to deal with them in a well structured, mitigated and supported manner.

Jonathan described Roche’s global system in which local information and global information are combined:
- Data is collected continuously, not just during audits, from all sources (including informal questionnaires) to identify potential risks
- Data is analysed for impact by both operational and quality staff
- Audits are then used to discover or confirm risk and to validate this risk assessment process, even to confirm a low risk.
Gwynneth Weir, Senior Director of QA, Quintiles chaired the workshop titled **Current and Emerging Quality Culture**.

After a brief introduction to the session, groups were asked to brainstorm ideas concerning how to incorporate a quality culture into an organisation. After presenting their ideas to the meeting each group developed one towards a workable strategy.

Participants were from different GxP environments but had experienced similar issues and they suggested some innovative resolutions.

In closing, Gwynneth shared some of Quintiles’ initiatives to optimise a quality culture, such as management ownership of the quality culture; identifying QA global leads for projects and functions; quality planning team meetings and monthly quality review meeting.

**Hot Topics** raised were mainly GCP related; of note was a discussion on the increasing demands of the monitor. The prevailing trend seems to involve reinterpretation of GCP resulting in greater expectations; for example, replication of steadily more facility records in study files.

Significant efforts from volunteers enabled the seminar and this report. All are appreciated greatly and more opportunities (for volunteering and valuable professional development) are available. Planning for 2012 is underway…

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**Keynote address from the National Research Ethics Service (NRES), National Patient Safety Agency**

Sandra Holley, Head of Quality Assurance

**‘The NRES Quality Management Programme’**

**Presentations**

- Why do similar audit findings continue to come up during subsequent audits?
- Electronic Documentation

**Hot Topics**

- GLP
- GCP
- GMP

**Plus**

Networking Quiz

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**The forum will be hosted by Premier Research, Wokingham**

For more information, to book online or download a manual booking form visit the BARQA website.

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**If you have a hot topic or a question to suggest please forward it to:**

Christine Henderson

chris henderson44@yahoo.co.uk
## BOARD & COMMITTEES

### BOARD

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<td><a href="mailto:rachel.hodges@astraZeneca.com">rachel.hodges@astraZeneca.com</a> or <a href="mailto:chairman@barqa.com">chairman@barqa.com</a></td>
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<td><a href="mailto:louise@handyconsulting.co.uk">louise@handyconsulting.co.uk</a> or <a href="mailto:lhandy@barqa.com">lhandy@barqa.com</a></td>
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<td><a href="mailto:roj.baxendale@gsk.com">roj.baxendale@gsk.com</a> or <a href="mailto:rbxendalel@barqa.com">rbxendalel@barqa.com</a></td>
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<td><a href="mailto:angela.jennings@synequanon.com">angela.jennings@synequanon.com</a> or <a href="mailto:ajennings@barqa.com">ajennings@barqa.com</a></td>
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<td>REGIONS (BRITISH ISLES)</td>
<td>HANJIT LALL</td>
<td>01234 264799</td>
<td><a href="mailto:harjit.lall@unilever.com">harjit.lall@unilever.com</a> or <a href="mailto:hlal@barqa.com">hlal@barqa.com</a></td>
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<td>IMMEDIATE PAST CHAIR</td>
<td>ANDREW WADDELL</td>
<td>0131 450 7017</td>
<td><a href="mailto:andrew.waddell@tmqa.co.uk">andrew.waddell@tmqa.co.uk</a> or <a href="mailto:pastchairman@barqa.com">pastchairman@barqa.com</a></td>
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<tr>
<td>CHAIRMAN</td>
<td>SVEN BUCKINGHAM</td>
<td>01502 517183</td>
<td><a href="mailto:svenbuckingham@hotmail.com">svenbuckingham@hotmail.com</a> or <a href="mailto:animalhealth@barqa.com">animalhealth@barqa.com</a></td>
</tr>
<tr>
<td>SECRETARY</td>
<td>KARL BUTLER</td>
<td>01908 485324</td>
<td><a href="mailto:karl.butter@sp.intervet.com">karl.butter@sp.intervet.com</a></td>
</tr>
<tr>
<td>KAREN DE KEULENAER</td>
<td>Clinical Development Services</td>
<td>+32 498 538769</td>
<td><a href="mailto:karen.de.keulenaer@pandora.be">karen.de.keulenaer@pandora.be</a></td>
</tr>
<tr>
<td>JUDITH HUNTER</td>
<td>Pentlands Management Systems Ltd.</td>
<td>0131 440 9485</td>
<td><a href="mailto:judithhunter@pmsqa.com">judithhunter@pmsqa.com</a></td>
</tr>
<tr>
<td>JOANNE MCKEELIE</td>
<td>Evita Services</td>
<td>028 60 699215</td>
<td>jofevitas.eu</td>
</tr>
<tr>
<td>IAIN MCPHEE</td>
<td>Novartis UK Ltd.</td>
<td>01376 551222</td>
<td><a href="mailto:iain.mcphee@novartis.com">iain.mcphee@novartis.com</a></td>
</tr>
<tr>
<td>JANICE SARASOLA</td>
<td>Ondax Scientific</td>
<td>+34 943 646087</td>
<td><a href="mailto:sarasolal@ondax-scientific.com">sarasolal@ondax-scientific.com</a></td>
</tr>
<tr>
<td>BRIAN TIMMS</td>
<td>Animal Health and Veterinary Laboratories Agency</td>
<td>01932 357727</td>
<td><a href="mailto:b.timms@vla.defra.gsi.gov.uk">b.timms@vla.defra.gsi.gov.uk</a></td>
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<tr>
<td>CHAIRMAN</td>
<td>JOHN DIXON</td>
<td>07540 012857</td>
<td><a href="mailto:john.dixon@gartner.com">john.dixon@gartner.com</a> or <a href="mailto:computing@barqa.com">computing@barqa.com</a></td>
</tr>
<tr>
<td>SECRETARY</td>
<td>ANDREW WARD</td>
<td>01379 672371</td>
<td><a href="mailto:warda@ukorg.huntingdon.com">warda@ukorg.huntingdon.com</a></td>
</tr>
<tr>
<td>LIZ ADAMS</td>
<td>GlaxoSmithKline</td>
<td>01920 884352</td>
<td><a href="mailto:liz.a.adams@gsk.com">liz.a.adams@gsk.com</a></td>
</tr>
<tr>
<td>JOANNE DONALD</td>
<td>Patheon UK Ltd.</td>
<td>01793 501536</td>
<td><a href="mailto:joanne.donald@patheon.com">joanne.donald@patheon.com</a></td>
</tr>
<tr>
<td>MATTHEW JONES</td>
<td>Johnson &amp; Johnson PRD</td>
<td>01494 658592</td>
<td><a href="mailto:mjohnes15@its.jnj.com">mjohnes15@its.jnj.com</a></td>
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<tr>
<td>BARBARA KAY-FARROW</td>
<td>Covance</td>
<td>01628 548225</td>
<td><a href="mailto:barbara.kay-farrow@covance.com">barbara.kay-farrow@covance.com</a></td>
</tr>
<tr>
<td>JOHN MCNAMEE</td>
<td>Instem Life Science Systems Ltd.</td>
<td>0151 229 7701</td>
<td><a href="mailto:john.mcnamee@instem-lss.co.uk">john.mcnamee@instem-lss.co.uk</a></td>
</tr>
<tr>
<td>CHRISTOPHER MONTGOMERY</td>
<td>GASTS Ltd.</td>
<td>07702 602457</td>
<td><a href="mailto:christopher.montgomery@intitworld.com">christopher.montgomery@intitworld.com</a></td>
</tr>
<tr>
<td>MARIAN Mutch</td>
<td>Covance Pharmaceutical R&amp;D</td>
<td></td>
<td><a href="mailto:marian.mutch@covance.com">marian.mutch@covance.com</a></td>
</tr>
<tr>
<td>SARAH PICKERSGILL</td>
<td>Celerion</td>
<td>+33 9 79 17 79 09</td>
<td><a href="mailto:sarah.pickersgill@celerion.com">sarah.pickersgill@celerion.com</a></td>
</tr>
<tr>
<td>NICHOLA STEVENS</td>
<td>AstraZeneca</td>
<td>01625 518546</td>
<td><a href="mailto:nicola.stevens@astrazeneca.com">nicola.stevens@astrazeneca.com</a></td>
</tr>
<tr>
<td>THANABALAN SUBRAMANIAN</td>
<td>GE Healthcare Medical Diagnostics</td>
<td>01494 543310</td>
<td><a href="mailto:thanabalansubramanian@ge.com">thanabalansubramanian@ge.com</a></td>
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### EDUCATION & TRAINING

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<tr>
<td>CHAIRMAN</td>
<td>PETER DAVIES</td>
<td>0700 600640</td>
<td><a href="mailto:peter@peterdaviesassociates.com">peter@peterdaviesassociates.com</a> or e&amp;<a href="mailto:t@barqa.com">t@barqa.com</a></td>
</tr>
<tr>
<td>SECRETARY</td>
<td>TOMMY FARRELL</td>
<td>01625 512474</td>
<td><a href="mailto:tommy.farrell@astraZeneca.com">tommy.farrell@astraZeneca.com</a></td>
</tr>
<tr>
<td>DAVID BUTLER</td>
<td>Quotient Bioresearch Ltd.</td>
<td>01638 724313</td>
<td><a href="mailto:david.butter@quotientbioresearch.com">david.butter@quotientbioresearch.com</a></td>
</tr>
<tr>
<td>SIMON CLAYTON</td>
<td>Pfizer Global Research &amp; Development</td>
<td>01304 462503</td>
<td><a href="mailto:simon.clayton@pfizer.com">simon.clayton@pfizer.com</a></td>
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<tr>
<td>YASSER FAROQ</td>
<td>DSTL</td>
<td>01980 658295</td>
<td><a href="mailto:yfarooq@dssl.gov.uk">yfarooq@dssl.gov.uk</a></td>
</tr>
<tr>
<td>PETER KNAPP</td>
<td>PharmaNet Ltd.</td>
<td>01628 551214</td>
<td><a href="mailto:pknapp@pharmanet.com">pknapp@pharmanet.com</a></td>
</tr>
<tr>
<td>SU LEE</td>
<td>Asterand UK Ltd.</td>
<td>0173 211600</td>
<td><a href="mailto:su.lee@asterand.com">su.lee@asterand.com</a></td>
</tr>
<tr>
<td>LEE MONK</td>
<td>UCB</td>
<td>01753 447833</td>
<td><a href="mailto:lee_monk@ucb.com">lee_monk@ucb.com</a></td>
</tr>
<tr>
<td>SANJAY MOTIVARAS</td>
<td>Grunenthal Ltd.</td>
<td>01494 480376</td>
<td><a href="mailto:sanjay.motivaras@grunenthal.com">sanjay.motivaras@grunenthal.com</a></td>
</tr>
<tr>
<td>SARAH PENROSE</td>
<td>Smith &amp; Nephew Research Centre</td>
<td>01904 824178</td>
<td><a href="mailto:sarah.penrose@smith-nephew.com">sarah.penrose@smith-nephew.com</a></td>
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<td>GlaxoSmithKline CUC, ACCI</td>
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<td>LYNET SPENCER</td>
<td>Eurofins AgroScience Services</td>
<td>01332 864800</td>
<td><a href="mailto:lynespencer@eurofins.com">lynespencer@eurofins.com</a></td>
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<tr>
<td>CHAIRMAN</td>
<td>COLIN WILsher</td>
<td>01442 402344</td>
<td><a href="mailto:colin.wilsher@pfiizer.com">colin.wilsher@pfiizer.com</a> or <a href="mailto:gcp@barqa.com">gcp@barqa.com</a></td>
</tr>
<tr>
<td>SECRETARY</td>
<td>ANGELIKA TILLMANN</td>
<td>+49 6078 967 9293</td>
<td><a href="mailto:angeliika.tillmann@theorelmclinical.com">angeliika.tillmann@theorelmclinical.com</a></td>
</tr>
<tr>
<td>MARTHA BYRNE</td>
<td>NAPP Pharmaceutical Ltd.</td>
<td>01223 397514</td>
<td><a href="mailto:martha.byrne@napp.co.uk">martha.byrne@napp.co.uk</a></td>
</tr>
<tr>
<td>ROSEMARIE CORRIGAN</td>
<td>Norgine Ltd.</td>
<td>01859 453644</td>
<td><a href="mailto:rcorrigan@norgine.com">rcorrigan@norgine.com</a></td>
</tr>
<tr>
<td>PATRICIA HENLEY</td>
<td>London School of Hygiene and Tropical Medicine</td>
<td>0207 9272625</td>
<td><a href="mailto:patricia.henley@lshmm.ac.uk">patricia.henley@lshmm.ac.uk</a></td>
</tr>
<tr>
<td>BARNEY HOBBS</td>
<td>Novartis Pharma AG</td>
<td>+44 61 696 8215</td>
<td><a href="mailto:barney.hobbs@novartis.com">barney.hobbs@novartis.com</a></td>
</tr>
<tr>
<td>KEITH MILLER</td>
<td>Johnson &amp; Johnson PRD</td>
<td>01494 658875</td>
<td><a href="mailto:kmill@15its.jnj.com">kmill@15its.jnj.com</a></td>
</tr>
<tr>
<td>SIMON MOLLOY</td>
<td>Gilead Sciences Ltd.</td>
<td>01223 897437</td>
<td><a href="mailto:simon.molloy@gilead.com">simon.molloy@gilead.com</a></td>
</tr>
<tr>
<td>ANGELA REPA</td>
<td>Novartis Vaccines and Diagnostics</td>
<td>+31 20 5640317</td>
<td><a href="mailto:angela.repa@novartis.com">angela.repa@novartis.com</a></td>
</tr>
<tr>
<td>GLENE SANDOM</td>
<td>Icon Clinical Research (UK) Ltd.</td>
<td>01628 496377</td>
<td><a href="mailto:glene.sandom@iconplc.com">glene.sandom@iconplc.com</a></td>
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<tr>
<td>BRUCE SEYMOUR-TAYLOR</td>
<td>Seymour-Taylor Consulting Ltd.</td>
<td>01844 278660</td>
<td><a href="mailto:bruce@seymourtaylorconsulting.com">bruce@seymourtaylorconsulting.com</a></td>
</tr>
<tr>
<td>CHRIS SHEPHERD</td>
<td>GlaxoSmithKline</td>
<td>0208 9904427</td>
<td><a href="mailto:chris.j.shepherd@gsk.com">chris.j.shepherd@gsk.com</a></td>
</tr>
<tr>
<td>MICHAEL SMITH</td>
<td>MSD Ltd.</td>
<td>01992 455246</td>
<td><a href="mailto:michael.smith30@merck.com">michael.smith30@merck.com</a></td>
</tr>
<tr>
<td>MONJIT SUMMY</td>
<td>Shire Pharmaceutical Development Ltd.</td>
<td>01256 894516</td>
<td><a href="mailto:monjitsummy@shire.com">monjitsummy@shire.com</a></td>
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<td>KATH WILMITH</td>
<td>Leo Pharma</td>
<td>01844 347333</td>
<td><a href="mailto:kath.williams@leo-pharma.com">kath.williams@leo-pharma.com</a></td>
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