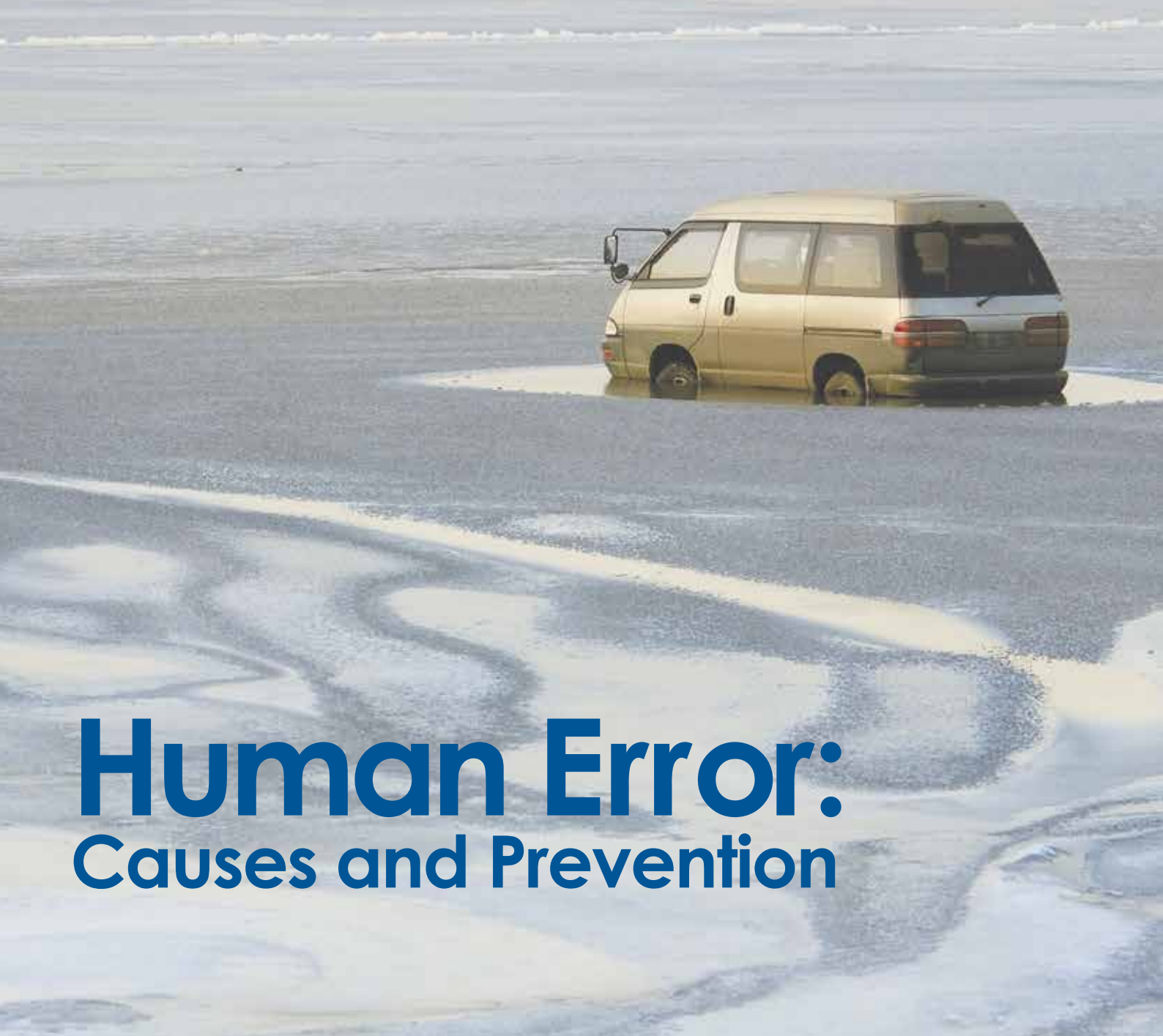


The Journal

Issue 26, Fall 2013



Human Error: Causes and Prevention



Health Sciences
Pharma
Biotech



www.nsf-dba.com



Neil Wilkinson
President, NSF Health Sciences Pharma Biotech

Welcome to the Fall edition of The Journal. I hope you have all enjoyed the traditional summer period (at least for those of us in the northern hemisphere) and enjoyed some quality time with friends and family, away from the day-to-day excitement, and demands, of the ever-changing pharmaceutical industry.

As mentioned in the last edition of The Journal, within NSF Health Sciences, the Pharma Biotech business unit is continuing on its journey to integrate our highly respected NSF-DBA and Becker & Associates legacy companies.

NSF Health Sciences



We will officially become the NSF Health Sciences Pharma Biotech business unit in January 2014, at which point the DBA and Becker names will be consigned to the history books. We will however strive to maintain, and improve, the values, traditions and high quality services we offer in consulting, auditing and education/training programs to individuals and firms doing business with us.

NSF Health Sciences Pharma Biotech

President Neil Wilkinson		
DC Office	Boston Office	UK/EU Office
Executive Vice President Maxine Fritz	Vice President Janeen Skutnik	Vice President Martin Lush

The new business unit gives us the opportunity of offering our clients, both old and new, a broader range of services and more global coverage. Our services will include:

Consulting

- Corporate compliance
- Quality management
- Remediation activities – US and EU
- Inspection readiness
- Due diligence
- Regulatory strategy and submissions
- Technical consulting (e.g. steriles, formulation, facilities, etc.)

Auditing

- Third-party audits of CMOs, labs, suppliers, distribution, etc.
- IPEA excipient audits and certification
- Consultative audits
- Due diligence
- Mock inspections – FDA, EU

Education and Training

- In-house modular programs for firms
- EU Qualified Person (QP)
- Pharmaceutical audit and self-inspection (IRCA)
- Public training course programs – UK/EU/US
- Webinars

Moving back to The Journal, we previously published two separate versions—one for the UK/EU and one for the US. Starting with this edition, we are now publishing one all-inclusive global journal. In this issue, we have included further thoughts on a topic that still remains high on people’s agendas, both from an operational excellence perspective and as a regulatory area of focus – that of human error and its prevention. The mass classification of the cause of problems into a “human error bucket” is often a lazy way of closing investigations – why not also add “retrain the operator and revise the SOP” as a corrective action? This all needs a complete rethink as human error itself is rarely a cause. The article on page 8 explores some of the potential contributory factors.

Closely linked to this concept, we present some thoughts on “training or education” (page 6). Training alone is not enough for a company to drive improvement. Educated staff at all levels and within all functions are needed within an organization for it to be successful by ensuring the right decisions are made and that levels of waste/the cost of (non) quality continue to be reduced. This theme is also reflected in the case study article on how an effective pharmaceutical quality system (PQS) can help a company improve and free up resources to focus on what matters (page 12).

In the Regulatory Update (page 19), we bring you the latest news on activities related to the implementation of FDASIA in the USA and FMD in the EU. As we predicted, these separate, but similar, pieces of legislation are now beginning to have a major impact on how pharmaceutical manufacturing and supply will be conducted.

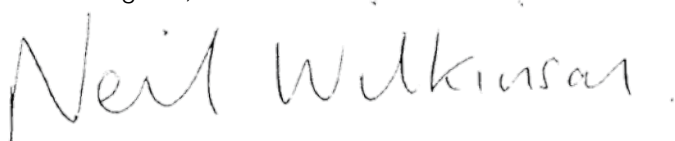
From ICH, we also bring you an update on ICH Q3D – Elemental Impurities Guidance (page 4), which has now reached the public comment stage. We outline the potential impact of this guidance, and how in parallel with USP activities in this area, it could impact you.

So, bringing together a strong quality culture, an effective PQS and an educated and trained workforce, which is current with today’s rapidly changing expectations, meets the need for meeting today’s global regulatory expectations. And, more importantly, it makes a powerful business case for assuring a healthy business that assures the quality and availability of medicines for our patients.

We remain passionate at NSF Health Sciences about working with our clients to help transfer the expert knowledge of our staff and associates to help individuals and companies prosper, and meet the ever-changing challenges of pharmaceutical development, manufacturing and supply today and into the future.

Please do not hesitate to contact us to discuss your needs for consulting, auditing and education/training programs.

Best regards,



Neil Wilkinson
President, NSF Health Sciences Pharma Biotech





Tech Talk

How to Prepare for the ICH Q3D Elemental Impurities Guideline

by Janeen Skutnik

The upcoming implementation of the International Conference on Harmonisation's ICH Q3D Guideline for Elemental Impurities and the United States Pharmacopeia (USP)'s General Chapters for Elemental Impurities has triggered its fair share of concern and uncertainty. Some of this is due to the unknown and some is due to a lack of clarity on how these guidelines will be applied to dosage forms and products that don't have a daily dose. The ICH Q3D document is currently at Step 2B, and will be published by the three regulatory regions for public consultation. While we now know the proposed Permitted Daily Exposures (PDEs) to apply, we don't have a complete picture of the levels present in all formulations. In line with ICH, we also have to contend with revisions to USP's General Chapters and their approach to elemental impurities. So what do companies need to do now to prepare?

We cannot just wait for the ICH Guideline to reach Step 4 and act then. We must prepare and act now.

What's Coming

Elemental impurities in finished drug products can come from several sources, including, but not limited to:

- Intentionally added (typically catalysts) in synthesis
- Present as contaminants (interactions with processing equipment)
- Inherent in components/ingredients (naturally occurring from mined excipients for example)

The guideline contains three main aspects:

- An evaluation of the toxicity data for potential elemental impurities
- The establishment of PDEs for each element of toxicological concern
- Development of controls to limit the inclusion of elemental impurities in drug products to levels at or below the PDE

The guideline breaks the various elemental impurities into four different classifications:

- Class 1: (As, Cd, Hg and Pb): Highly toxic across all administration routes. These require special consideration during the risk assessment, due to their high toxicity and the potential for them to be present in finished dosage form through contributions of naturally derived materials.
- Class 2: Toxic to a greater or lesser extent based on route of administration.
- Class 3: Relatively low toxicity by oral route of administration, but require consideration in the risk assessment for other routes of administration.
- Class 4: Elemental impurities that have been evaluated but for which a PDE has not been established due to their low inherent toxicity and/or regional regulations.

The guideline can be boiled down to four simple steps:

1. **Identify:** Identify the sources of elemental impurities that are known or suspected, or have the potential to end up in the finished product.
2. **Analyze:** Determine the probability of occurrence of the elemental impurities in the finished dosage form.
3. **Evaluate:** Assess the actual or predicted levels of elemental impurities with the established PDEs.
4. **Control:** Develop, document and implement a plan to limit the elemental impurities in the finished dosage form.

A key point that many in the industry have overlooked is the fact that the USP implementation will only apply to finished products with monographs. So that means manufacturers of products like toothpaste and talcum powder can breathe a sigh of relief, while most manufacturers of prescription and over-the-counter medications need to be prepared for the guidelines. But how do you prepare for the unknown? The

ICH guideline will apply initially to all new products as defined within the scope of the consensus draft. So manufacturers need to carefully monitor both USP and ICH activities to determine the impact to their specific product line.

How to Prepare

Pharmaceutical companies need to begin preparing now:

- **Determine the impact.** Begin to assess your products and what levels of elemental impurities they contain, remembering that the USP's implementation of elemental impurities will impact existing drug products from the enforcement date

- ❖ **Consider all the potential sources of elemental impurities:**

- ❖ Contributions from elemental impurities that are intentionally added to reactions or processes leading up to the preparation of the drug substance, reagents, starting materials or excipients (e.g. metal catalysts)
- ❖ Those that are known or suspected to be present in the drug substance, reagents, water, starting materials or excipients used in the preparation of the drug product (e.g. lead present in a mined excipient)
- ❖ Those that are known or suspected of being introduced into the drug substance or drug product from manufacturing equipment
- ❖ Those that are known or suspected of being leached into the drug substance and drug product from container closure systems

- **Engage in discussions with your regulators.** Having open conversations with the appropriate regulatory agencies is an important step in compliance with any new guideline

- **Prioritize according to risk.** Since most companies are scrambling to address this issue and may not be ready by the time the USP chapter is implemented, I suggest companies prioritize their efforts based on patient/consumer risk. For example, you might want to start with injectable products, then move on to orals and save topical and transdermal products for last. It is advantageous to develop an implementation plan and strategy that documents how your company will address the requirements

- **Develop a compliance strategy and proactively share it with your regulators.** After you've developed your compliance strategy, go to the FDA and proactively explain how you are planning to comply with the new guidelines. Include a timeline with key milestones for each product category. Typically, regulators are receptive to these discussions and may be able to provide helpful guidance to modify your plan

- **Engage in discussions with your suppliers.** Start having open conversations with your suppliers about the need for data (where available) on the levels of metals present in materials. Consider using tools developed by the International Pharmaceutical Excipients Council of the Americas (IPEC) in order to focus on the right questions. Don't just send out questionnaires and expect your suppliers to return them and comply. **Keep in mind, suppliers don't need to comply with the guidelines; manufacturers of finished products need to comply.** It's also important to include representatives from your company's quality and compliance organizations in these discussions with suppliers. Don't simply delegate the task to the procurement function

- **View suppliers as partners.** It's worth noting that most suppliers of excipients don't really need the additional complexity of dealing with the pharmaceutical industry! Most excipient manufacturers are not manufacturing materials primarily for the pharmaceutical industry. And, typically, the pharmaceutical industry isn't the largest buyer of their materials. For example, only .02 percent of cellulose is used in pharmaceutical products. This presents a special challenge – and the need for a bit of diplomacy – as we work with suppliers to meet our regulatory requirements

The bottom line: The pharmaceutical industry has a lot of work to do in the next 10 to 12 months to prepare for these new elemental impurities guidelines. There's no time to waste and no sense in burying your head in the sand. Rather than waiting for the FDA or EMA to tell you what to do, manufacturers of finished dosage products must be proactive and start now in a genuine effort to better understand and control elemental impurities in their products.



Janeen Skutnik is a Vice President at NSF Health Sciences, Pharma Biotech, a division of NSF International. We have more than 30 years of experience in consulting, training and auditing services for the pharmaceutical industry. She can be reached at jskutnik@nsf-dba.com

Education vs. Training:

Education is what remains when the training

We all know your products are only as good as the people involved in making them. It goes without saying that how you educate your people is vital to your success. At NSF Health Sciences, we talk about education, not training. For us they mean two very different things: You educate your children and train your pets. Of concern to us is that many companies still resort to traditional (in some cases, tick-box) training methods – rather than educating staff at all levels for lasting improvement. For us, understanding the **WHY** is critical in performing any task/ making any decision.

Some startling facts about traditional training:

- Most pharma companies still use the traditional approach to training where participants sit in a classroom looking at PowerPoints, listening to the course presenter. Although quick and easy, this traditional approach can be very ineffective – its success depends totally on having experienced, savvy, knowledgeable tutors. Without such tutors it does not improve understanding and does little in changing behavior. In fact, most participants forget almost 90 percent of the subject matter within 24 hours of leaving the classroom. This tick-box approach to training also creates an alarming false sense of security. You think your people understand what they have to do and can apply this knowledge in the workplace... when they can't
- Did you realize that most of us use only 7 percent of our intellectual capability? The worrying thing is that the figure is actually falling as schools and universities resort to cramming more facts into young brains, rather than teaching them how to think. Most companies have simply not tapped into the intellectual capability of their workforce, and yet their future depends upon it. In many organizations at all job levels the level of “what you don't know” impacts directly upon the decisions made. Remember – you don't know what you don't know! Firms often talk about people being their biggest asset – but do they back this up with actions to ensure a well educated workforce?
- Most people have a maximum attention span of 20-30 minutes. If traditional training sessions extend beyond this without a break or change of activity, you may as well not bother, as most people have switched off by then
- All learning is state dependent. If participants are not in the mood for learning, they will not learn anything. The right environment needs to be created – keep participants free from the routine daily distractions and work related interruptions – do not disturb!
- Everyone has a preferred learning style. Unless education methods match individuals' learning styles, nothing will sink in and behaviors will remain unchanged. A variety of styles may be needed to engage a group
- For any training to be effective, it must be personal and relevant to those involved. There is no such thing as a one-size-fits-all approach
- Good education and training can seem expensive – but getting things wrong, as we see daily in our industry, can be far more expensive – the cost of poor quality/poor decisions, the risk of regulatory actions, the reputational damage... and worst of all – the potential impact on our patients. As the old saying goes... ‘If you think education is expensive, try ignorance’.

What Is the Difference?

has been forgotten

By Martin Lush and
Neil Wilkinson

Moving from Training to Education: How We Can Help

We are developing a **'From Trainers to Educators'** workshop. Our objective is simple: to turn your trainers into effective educators by giving them the skills and competencies to change behaviors and improve performance in the workplace.

What We Cover

- How adults learn and how to use this information to design “brain-friendly” sessions that change behaviors and improve performance
- How to ditch “death by PowerPoint” to make sessions more interactive, fun and engaging. After all, effective learning is an active process, not a spectator sport
- How to take education out of the classroom and into the workplace
- How to apply rapid learning techniques so that you can cover more in less time, and change behaviors

How We Teach: Our Education Philosophy

- We focus on explaining the why to underpin the how. Understanding the consequences for getting it wrong builds problem-solving skills and encourages personal ownership of activities and behaviors
- We break down information into manageable sections, take breaks and switch between activities to keep people interested
- We encourage people to stay focused on learning by maintaining high levels of interaction by using customized case studies and problem solving exercises. Only by practicing new tools and techniques can behaviors change
- Our courses appeal to every learning style including kinesthetic, auditory and visual

During this workshop, you will actually design education programs that you can then roll out across your company.

These workshops are customized to meet your exact needs and requirements to ensure that you have the educated workforce upon which your future depends. If you would like more information on how to transform your trainers into educators, please call us.



Why Intelligent People Organizations Do Irra

As a leading consultancy and training provider to the pharma, biotech and devices industries, we are privileged to work with people who are both motivated and smart. In fact, our industries employ more PhDs and graduates than many other sectors! Yet, when you read through some recent 483s, you are left wondering why respected organizations, staffed with intelligent people, do some very illogical things. Take for example these recent non-compliances:

- “393 customer complaints that had not been investigated”...
- “Widespread SOP non-compliance...” companies spending millions of dollars on writing SOPs that are too complicated to use...
- “Audible alarms switched off”...
- “Risk assessment used to justify poor practices”...
- “Ineffective and under-resourced training programs”...
- “Absence of planned maintenance program (breakdown only!)”...
- “Over reliance on poorly trained contractors”...

So why do organizations with a collectively high IQ do such things? Why is common sense not always translated into common practice? Over the last 27 years, NSF Health Sciences has gained an enviable reputation helping companies improve compliance, efficiency and decision making. Here are some reasons (contributing factors) why we think intelligent people do strange things. Any sound familiar?

Contributing Factor 1: Institutional Arrogance

A good compliance history combined with impressive business growth can, in our experience, lead to a false sense of security. Even institutional arrogance. This apparent lack of failure can be dangerous since failure acts as an emergency stop that forces companies and individuals to reassess what they do, learn from the experience and move on. The absence or suppression of any failure results in organizations believing their own propaganda. Critical thinking and analysis stops only to be replaced with arrogance and complacency which then leads to poor decision making. This is where an open and honest culture, supported by robust governance processes and structures, is vital.

Contributing Factor 2: Institutional Bad Habits (Acting Without Thinking)

People and organizations are creatures of habit (acting without conscious thought). One company habitually ignored its change control system because of its overwhelming complexity. Most engineers habitually used the emergency change control system without thinking. Bad habits can creep in due to a number of reasons:

- Lack of educated personnel who understand the why that underpins the how, particularly in leadership and supervisory roles ultimately responsible for standard setting. They don't know how to set a good example
- Leadership disconnected from the shop floor, with managers who have forgotten what MBWA stands for (management by walking about)
- Leadership failing to walk the talk and live the values of the company
- Performance measures that drive the wrong behaviors and habits. Encouraging people to reduce deviations by n% creates a mindset that deviations are “bad”
- Insensitive or inadequate internal surveillance systems. Good audit, self-inspection, deviation and CAPA systems are vital in detecting and correcting bad habits
- Governance processes and behaviors that regard quality metrics and reporting as a “beauty contest” between departments and sites
- Peer pressure and group think. Bad habits are recognized but not addressed due to peer pressure or group-think that leads to justification of bad practices
- Inward thinking and failure to benchmark against external standards and improvement in best practice

Contributing Factor 3: Ignorance Due to Poor Education

Many bad decisions and inappropriate behaviors can be due to people at all levels in the organization not knowing any better. This can happen when companies invest in training rather than education. Remember, we educate our children and train our dogs. If we apply a pure training approach to people, we end up with a workforce that knows what buttons to press without knowing why or understanding

e In Respected tional Things!

By Martin Lush

the consequences for getting it wrong. When people are educated to know these things, they take personal ownership for their activities and behaviors. More than this, only then can their full potential be realized and the company benefit from the intellectual capital that is present in the workforce. This is a prerequisite for any continuous improvement activities.

Contributing Factor 4: Culture of Fear and Blame

Continuous improvement needs an educated workforce but it is only possible when people have the freedom to challenge the status quo, bringing problems to the surface for sharing with all, no matter where they are in the organization. When blame and fear exist, problems remain, issues are hidden and bad practices go unchallenged. Without openness and transparency, continuous improvement and management of risk is impossible, corporate governance is doomed to failure and the working environment becomes “toxic”.

Contributing Factor 5: Systems That Encourage Bad Practice and Poor Decision Making

System complexity and inappropriate design can encourage people to do crazy things. Some examples include:

- Excessive signatures in a batch record leading to signatures being completed after the task rather than during
- Overly complicated batch documents encouraging poor aseptic practice in the cleanroom
- Poor equipment design leading to excessive interventions
- Poor staffing levels in the cleanroom resulting in rushing around and poor aseptic practice
- SOPs that are so complex they can't be used, leading to inconsistent practice

Contributing Factor 6: Lack of Personal Integrity and Honesty

On very rare occasions, bad practice and inappropriate behaviors come down to the individual. People do things they know are wrong because they are either dishonest or lack personal integrity. Poor decision making on the part of individuals can also be attributable to the following:

- They simply don't care and have very little pride in what they do. In our experience this is often the fault of the company rather than the individual. When companies care little about their employees, the culture can impact the behavior of individuals by creating a predominating mentality of “If they don't care about me, why should I care about what I do?”
- Previous experience in another company
- Arrogance can also be a contributing factor, with thinking like:
 - I know best
 - I am beyond the law; the rules don't apply to me
 - I won't get caught



Why Intelligent People In Respected Organizations Do Irrational Things!



Contributing Factor 7: Hierarchy

Hierarchy, where group members are distinguished by seniority and power, is evident in every society, let alone company. Hierarchy can be both constructive and destructive in equal measure. Best-in-class companies have an enabling hierarchy and focus on engaging the entire organization to drive personal ownership of quality and personal responsibility for continuous improvement. Underpinned by effective education, this can be achieved using a number of mechanisms symbolic of a healthy and productive hierarchy that uses the talent of the entire workforce. For example:

- Quality circles
- Operator-led problem solving and continuous improvement initiatives
- Performance management objectives for quality and continuous improvement
- Operator-led self-inspections
- Suggestion schemes

Unhealthy hierarchies achieve the complete opposite and can lead to problems going unnoticed. They create a culture where people “know their place” and do not question authority or offer suggestions for continuous improvement. These companies are already on the path to failure.

Contributing Factor 8: Poor Performance Management Coupled With a Poor Attitude to Problems

Best-in-class companies have performance management systems that drive the right quality behaviors and practices, emphasizing that quality is the responsibility of all. In contrast, poor performance management systems can inadvertently drive the wrong behaviors:

- Under-reporting of deviations and incidents
- Problems and deviations being seen as bad
- Having to complete all investigations in the “magical” 30 days
- Failure to drive continuous improvement

Best-in-class companies drive continuous improvement by focusing on the performance measures and behaviors required as a result of a thorough analysis of problems and mistakes. These companies understand the potentially destructive nature of poorly defined measures and ineffective

and misdirected management review processes. Best-in-class performance only happens when problems, mistakes and deviations are seen as learning opportunities, and are investigated at the time they occur (not 29 days later...), rather than as painful embarrassments.

Contributing Factor 9: Overthinking

Educated and intelligent people can use misplaced logic to rationalize bad practice. This is commonly seen in companies that use risk assessment to justify what common sense tells them is wrong. Inappropriate behavior and bad decision making due to overthinking can be encouraged by many of the other contributing factors mentioned earlier.

Contributing Factor 10: Panic, Stress and Fatigue

People can do crazy things when under stress. As humans we are conditioned to fight, flight (run away) or freeze (do nothing) when threatened. This can result in people making decisions they would not normally make. Many of the contributing factors discussed earlier can be observed in corporate cultures that engender stress, panic and fatigue. These effects hinder good governance and controls. Regulatory inspections are very stressful for most people and inappropriate responses to inspectors can be given due to stress. Better planning and preparation in advance of any regulatory inspection can address these issues.

In general, people make the best decision available to them at the time. When intelligent people do crazy things it is usually due to a number of contributing factors which companies can address or avoid.

If you would like to find out more about Human Error: Causes and Prevention

- 1) call our UK or US office for advice/consultancy
- 2) come to one of our courses:
 - September 18-20, 2013 – The Netherlands
 - November 28-29, 2013 – Italy
 - February 4-5, 2014 – US
 - April 30-May 2, 2014 – UK
 - September 3-5, 2014 – The Netherlands
 - September 16-17, 2014 – US
- 3) **ask for us to undertake an in-house course for you – at your site, focused on your case studies**

For more information on our services on Human Error Reduction contact us at Pharma@nsf.org



Human Error Reduction Program

Reducing human error through long term partnerships with client companies

Methodology

Our methodology is intended to be simple, effective and transferable to client Subject Matter Experts. The workshop structure allows this program to exist alongside and augment other initiatives in companies such as LEAN, CAPA and Investigation Courses.

Structure 3 Core Workshops

- > **100.** Foundation for Error Reduction (1 day)
- > **200.** Investigative Technique for Error Avoidance (1 day)
- > **300.** Proactive Approaches for Error Avoidance (1 day)

100-300 Certification Program

Each workshop includes a course assessment to evaluate competency and knowledge acquisition however the NSF Human Error Reduction Program certification includes a post course tutor review of at least three CAPA or Proactive Analyses which meet specified effectiveness criteria.

1,000 Foot Overview Workshop

This one day course covers elements of each workshop in order to ensure that managers and supervisors will understand the full program, core concepts and be ready to embrace the projects that are taken on by subject matter experts.

10,000 Foot Overview Workshop

Intended for senior leadership, this half day course is a high level overview to set expectations and give advice on how to support the program to ensure sustainability and achieve the business results envisioned. The course can be extended to include case studies on systemic failures for senior leaders.

On Site Assessments

NSF is available on a consultancy basis to complete proactive assessments of unit operations following the Proactive Error Analysis model. It is a DMAIC approach focused on identifying opportunities for error reduction and elimination. These are often extended (week long) engagements managed on a consultancy basis.

Coaching/Mentoring

NSF tutors are available to answer questions as part of a long term agreement with our clients at no additional cost depending on the ongoing demand. Retained consultancy support is an approach which maximizes the partnership.

In House Certification

Upon achieving training and certification, NSF will certify in house trainers, allowing the company to stand alone and sustain the program while meeting agreed standards. Retained consultancy support of in house trainers maximizes their success during the initial phase of certification.

For more information, contact Pharma@nsf.org or visit www.nsf.org

Does Your Pharmaceutical Quality System Improve Your Competitive Edge?

By Martin Lush

Some Case Studies

Reducing Product Rejects: How Your PQS Can Help

One company reduced its rejects from 11 percent to 3 percent across all key brands, and from 3 percent to 0.001 percent on its high-speed syringe filling lines.

Achieved by:

- Better process control with greater investment in Statistical Process Control (SPC), which required an additional investment in new equipment
- The company improved the quality of its raw materials by moving away from cheaper suppliers and improving its auditing and management of third parties. Instead of treating them as contractors, the firm now considers them to be partners and simply an extension of its production line. Its auditors have all been certified to ensure consistency in auditing approach so they can have confidence in audit findings
- Problems (deviations) are now resolved within hours, not weeks. With our help, the deviation reporting system has been completely reengineered to allow incidents to be reported and triaged (risk ranked) within two hours of any deviation incident. Investigations now start within three hours, not 30 days! Investigations now focus on preventing recurrence and using every deviation incident to drive continuous improvement. Following an extensive education program in problem solving, the attitude to deviations has now changed. Every deviation is now considered to be an invaluable learning opportunity, rather than an inconvenience
- In the bad old days of high batch rejects, the company concentrated on starting a new batch *immediately* after a rejected one. This has now stopped. A cross functional team now completes a forensic style analysis of every batch reject to find out "why" *before* manufacturing the next batch. The outcome of the investigation, the Product Failure Investigation Report, is circulated widely across all divisions to share learning points

Reducing Reprocessing and Rework: How Your PQS Can Help

Another of our clients used its PQS to help reduce reprocessing and rework. The worst performing lines reduced rework from 22 percent to 7 percent.

Material Waste/Scrap: How Your PQS Can Help

When you have a robust and efficient PQS, you can drastically reduce unnecessary material waste and scrap. We helped one client reduce material waste from \$1.5 million to less than \$25,000 in just 18 months.

Production Lead Times: How Your PQS Can Help

Extended and prolonged lead times are symptomatic of an inefficient PQS. Back in 2009, one of our clients had a 15-day lead time for its number one liquid product. One day was taken for manufacture, three days for testing and 11 days to collate and review the batch record and release the



Remember, your Pharmaceutical Quality System is a Business Manager

There are some companies who believe that their Pharmaceutical Quality System (PQS) exists purely for regulatory compliance. We think this attitude is outdated and plainly wrong. At NSF-DBA, we believe that your PQS has only one purpose: **to improve your competitive edge** by guaranteeing the manufacture of high quality medicines at the lowest possible cost. We have worked in partnership with many of our clients to help them improve their PQS and their competitive edge. The following results give you a flavor of what can be achieved and how. Please contact us if you would like more information on how to use your PQS to improve your competitive edge.

product. We helped the client to reduce the lead time to just five days by helping simplify its batch record and product release procedures.

Plant and Equipment Utilization: How Your PQS Can Help

One client improved utilization of its oldest plant from 71 percent to 90 percent and equipment utilization from 52 percent to 74 percent.

Achieved by:

- Relying less on contractors
- Developing greater in-house engineering skills and competencies
- Adopting a rigorous risk-based approach to reliability-centered maintenance

Fast and Efficient Change Management: How Your PQS Can Help

We believe that good change control is a core competency for the future. The ability to quickly and effectively review and approve changes is absolutely vital in a fast changing marketplace. One of our clients recognized their change control system was so slow and complicated it was actually dangerous... people were working around it! With our help they simplified their change control system with dramatic results:

- The company's change control policy was simplified from 60 pages that nobody read to just 6 pages that people now do
- In the bad old days it took 40-60 days to get approval for a change request. Now it takes 30 minutes. The saving in man hours paid for the improvement program in just 6 weeks
- They now reject about 40 percent of change requests (they used to approve everything). This means they can

focus on implementing important changes effectively rather than doing everything badly

- Over 90 percent of approved changes are now implemented effectively. Before the improvement program less than 10 percent of approved changes actually delivered any return on investment

Moving from Risk Assessment to Intelligent Risk Management: How Your PQS Can Help

We believe that intelligent risk management is another core competency without which companies will not survive. One of our clients based their risk management policy on ICH Q9 but actually only practiced FMEA which was used reactively, when things went wrong. Following our education program on risk management:

- They now apply risk based thinking in almost everything they do. It has become a way of thinking, not a tool
- Risk management is now used more proactively, rather than reactively. It is used to prevent problems and has reduced costly fire fighting

Most companies are faced with the same challenge. Manufacturing high quality, regulatory compliant products at the same time as reducing costs. Cost reduction has traditionally focused on manufacturing operations, leaving the PQS well alone. As evidenced by these results, simplifying your PQS can dramatically improve your efficiency and reduce costs. If you are interested in improving your PQS to:

- Reduce reworks, reprocessing and waste
 - Reduce production lead times
 - Stop repeat deviations and use problems to drive continuous improvement
 - Improve plant and equipment utilization
 - Simplify your change control and documentation systems
- please give us a call.

Forthcoming Courses

Early Bird or Second Delegate discounts apply to some of our courses.
Please visit our website, www.nsf-dba.com, for full details



Sterile Products Manufacture

Amsterdam Marriott Hotel, Amsterdam, The Netherlands



October 7-10

Sterile products manufacture represents the most hazardous activity (to the patient!) performed by pharmaceutical companies. This is why it attracts so much regulatory scrutiny! Recent regulations and guidelines from EU (Annex 1) and FDA 'Sterile Drug Products Produced by Aseptic Processing' are confusing to many and very difficult – and expensive – to comply with in full.

This course is designed to help you comply with these and other documents in a way that is...

- Practical
- Scientifically sound
- Cost-effective

Course Fee: £2400.00 plus VAT

How to Perform Effective Product Quality Reviews

Manchester Marriott Victoria & Albert Hotel, Manchester, UK



October 8

This course is designed to assist you and your company in producing Product Quality Reviews which meet GMP expectations in an efficient manner that will add VALUE to your business as well as compliance to your operations. We will cover:

- The regulatory requirements for medicinal products and Active Pharmaceutical Ingredients in the EU and USA
- The data that should be included in a Product Quality Review and what may be excluded
- Statistical techniques to enable you to analyze and interpret data effectively
- How to decide if a process is in control, capable and still valid
- How to produce Product Quality Review reports which add value to your business and meet all regulatory expectations

Course Fee: £700.00 plus VAT

Satisfying Regulatory and Quality Requirements in Key Emerging Markets



NSF-DBA Boston Office, Boston, MA, USA

October 8-9

This course will provide an overview of the regulatory history, climate, and cultural drivers in the BRIC countries and other locations such as Turkey, Mexico and key Middle Eastern states. For instance, China (SFDA) and Brazil (Anvisa) regulatory bodies were only established in 1999; however agencies are changing rapidly and collaborating with other well established regulatory bodies. The pace of change and the regulatory trends driven by actions in the BRIC states must be appreciated. These countries are issuing GMP guidances with clear national compliance expectations and are increasingly demanding pre-approval inspections of export markets to gain access.

Course Fee: \$1775.00

Pharmaceutical Legislation Update: Continuing Professional Development for Qualified Persons & Technical Personnel



Manchester Marriott Victoria & Albert Hotel, Manchester, UK

October 9

The Qualified Person and other technical personnel need to be informed and aware of pharmaceutical legislation. Changes in legislation and guidelines, and the interpretation of them, can have significant implications for the individual and their company. The course will cover:

- The reality and interpretation of recent and new EU legislation
- Changes to EU GMPs
- An update on ICH and other international initiatives
- USA changes to legislation and FDA guidance
- UK updates

Course Fee: £700.00 plus VAT



Visit www.nsf-dba.com for more information on all our courses

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

What's planned for October – November 2013



GMP for Clinical Trials Manufacture and Supply



Park Hotel Amsterdam, Amsterdam, The Netherlands

October 14-17

The specific requirements and areas of Regulatory focus for the manufacture of Clinical Trial Supplies are explained and discussed in this course. Questions such as:

- Does the Falsified Medicines Directive apply to Clinical Supplies?
- How much validation is required and how soon?
- How can the QP ensure effective blinding when the sponsor determines the study design and protocol?
- What GMP implications will there be for the new Clinical Trial Regulation in 2016?

are not straightforward and require those involved to fully understand the risks and regulatory implications. Our team of highly experienced tutors, including ex-MHRA GMP inspectors, will discuss the answers to these questions and explain the pitfalls and weaknesses still seen in many companies manufacturing and supplying clinical materials.

Course Fee: £2400.00 plus VAT

Sorting out the Myths from the Facts of Supply Chain – Realities for Implementation of EU and US Legislation



NSF-DBA Boston Office, Boston, MA, USA

October 15

Globalization has had a major impact on the pharmaceutical industry. As companies have become more global, regulatory systems and company processes haven't necessarily evolved to take into account the increased complexity in the global supply chain. The growth of outsourcing, often to countries with less mature pharmaceutical industry understanding and regulatory systems, has also been significant as companies seek to lower their costs of operating.

This course will help you navigate the maze of new regulations, legislation and expectations from global regulators by covering the proposals from the regulators, the responses from the pharmaceutical industry, its suppliers of excipients and APIs, and related associations, along with good industry practices for 'end to end' supply chain assurance.

Course Fee: \$950.00

How Packaging Provides a Competitive Advantage to Ensuring Supply Chain Integrity



WORK SHOP

NSF-DBA Boston Office, Boston, MA, USA

October 16

**Morning Session, 08:30 – 12:00:
Packaging Anti-Counterfeiting Measures**

This course will provide an overview of the current situation regarding counterfeit pharmaceutical products and a discussion of the use of packaging in detecting counterfeit products, including recent discussions regarding serialization. It will then consider reasonable expectations for an anti-counterfeiting program and the types of technologies available.

**Afternoon Session, 13:00 – 16:30:
Packaging Component Supplier Assurance**

This course will discuss key points for a packaging vendor qualification program. It will review specific issues on printed packaging materials, including fundamental information on printing technology, leading to a discussion of the cost of errors, where errors occur, and how they may be prevented or detected. This section will include hands-on exercises.

Course Fee: \$950.00

Pharmaceutical Law & Administration



QP

Hilton York Hotel, York, UK

October 21-25

Pharmaceutical law and administration is a key foundation knowledge requirement for all Qualified Persons (QPs). This is clearly spelled out in the relevant article of European Directives 2001/82/EC and 2001/83/EC and in the current Qualified Person Study Guide. A thorough understanding of the laws and legal processes, within Europe and beyond, is essential. This is equally true for other pharmaceutical technical managers. On this course we will cover:

- Why we have medicines laws and what they seek to achieve
- The laws and legislative processes within the EU which impact on medicinal products, and hence the role of the QP
- The UK medicines legislative framework
- US and other international pharmaceutical legislation
- Other relevant laws and guidelines

Course Fee: £3200.00 plus VAT



Book your place on any of these courses, visit www.nsf-dba.com

Forthcoming Courses

Early Bird or Second Delegate discounts apply to some of our courses.
Please visit our website, www.nsf-dba.com, for full details

Good Autoclave Practice

Amsterdam Marriott Hotel, Amsterdam, The Netherlands



October 29-31

A Comprehensive Course on the Practicalities of...

- Autoclave selection
- Cycle design
- Equipment qualification
- Cycle validation
- Ongoing performance monitoring and management

What You Will Learn

- Current regulatory expectations for steam sterilization
- Current European and US regulatory expectations for steam sterilization – how they differ and why
- How to qualify and validate effectively
- How to troubleshoot problems
- Best practices for monitoring and management of autoclaves

Course Fee: £1800.00 plus VAT

Effective Pharmaceutical GMP Audits and Self-Inspections

(An IRCA Certified Pharmaceutical QMS Auditor/Lead Auditor Course)

Park Hotel Amsterdam, Amsterdam, The Netherlands



November 4-8

Supply chain assurance is the key topic in our industry today. From starting material to patient, pharmaceutical companies are expected to be able to demonstrate control. Increasingly that means audit or justify why not! Regulators' expectations for the quality of audits and their work continue to increase. This course will prepare you to perform your best audit ever.

You will develop a toolbox of auditor skills from planning to execution and follow-up. This course provides the training required for the IRCA certified Pharmaceutical Quality Management System auditor and lead auditor certificate (satisfactory completion of the course exam and past course audit experience are required to gain certification).

Course Fee: £2600.00 plus VAT



Quality Aspects of the CTD

Hilton York Hotel, York, UK



November 11-14

The ever-increasing complexity of obtaining approval for drug products requires that companies provide high quality registration applications. To achieve this objective, it is essential that personnel in Regulatory Affairs, Research & Development, Manufacturing and Quality Assurance understand regulatory requirements and work together as an effective team. The ICH Common Technical Document (CTD) has brought the possibility of a global dossier many steps closer. This emphasizes the importance of getting it right first time.

This course is designed to provide attendees with a clear understanding of the regulatory process and technical data requirements for registration and subsequent manufacture of medicinal products. Although this course will primarily focus on EU aspects, consideration will be given to corresponding aspects in US submissions.

Course Fee: £2400.00 plus VAT

Free Seminar for Prospective QPs and Sponsors

Cheshunt Marriott Hotel, Broxbourne, UK



November 12

Since 1990, NSF-DBA and the University of Strathclyde have collaborated to present a structured modular course designed for people wishing to become Qualified Persons. This course is now recognized as the most successful and main route to QP education in the UK and increasingly in Europe. Attend if you are:

- Planning to train to become a QP
- Interested in maximizing your technical knowledge and value to your organization
- Responsible for QP training or technical development
- Interested in gaining a vocational MSc, Postgraduate Diploma or Certificate

or want to know more about sponsoring a QP.

Visit www.nsf-dba.com for more information on all our courses

What's planned for October – November 2013



Pharmaceutical Quality Systems: Best Industry Practice



Manchester Marriott Victoria & Albert Hotel, Manchester, UK

November 12-13

How good is your Pharmaceutical Quality System? Will it comply with the requirements of ICH Q10? Will it satisfy the ever increasing demands of global regulatory agencies? With increasing levels of Warning Letters and the like is your PQS at risk? How does your PQS compare with the best in class?

Over the last 25 years NSF-DBA has audited many thousands of quality systems, some bad, many good. We have also looked at how those in the aviation, micro-electronics and automobile industries manage quality. From this research we have identified industry best practices for quality management systems. By sharing these, this course will help you to strike the right balance between compliance and effectiveness, and achieve operational excellence.

Course Fee: £1400.00

Effective Quality Systems for Research and Development



San Mateo Marriott San Francisco Airport, San Mateo, CA, USA

November 12-13

This course will provide a blueprint for how much and how soon for each component of the quality management system. Too much too soon will overburden a research based company and too little too late will jeopardize product approval and put your company and potentially your patients at risk. This course is about 'getting it right' – understanding the full scope of the quality management system and integrating with the lifecycle model of pharmaceutical development to offer a phased approach to the implementation of quality management systems.

Course Fee: \$1,775.00

Extractables and Leachables Requirements in Pharmaceutical Development



NSF-DBA Boston Office, Boston, MA, USA

November 12

This course will provide an overview of E&L with regard to pharmaceutical packaging/container closure systems, processing equipment and devices for drug products including biologics. We will review the regulatory framework and explain why this area is getting so much attention. You will learn about material selection and the risks certain materials present from an E&L standpoint. You will also gain insight into the best practices for E&L testing.

Course Fee: \$950.00

Workshop – Best Practices for Deviation and CAPA Management



San Mateo San Francisco Airport, San Mateo, CA, USA

November 14

Morning Session, 08:30 – 12:00: Best Practices for Deviation Investigations

We will review key requirements for handling deviations and GMP investigations in pharmaceutical and biopharmaceutical operations. Applying risk-based approaches and triaging methodologies will ensure time is devoted to the most important and sensitive investigations. Best practices for deviation management are reviewed and discussed.

Afternoon Session, 13:00 – 16:30: Best Practices for CAPA Management

CAPA systems can overwhelm a facility if not well managed. We will review key components of a well-managed CAPA system. System weakness will be reviewed along with measures which will tell you whether your CAPA system is functioning for company benefit. Regulatory expectations for CAPA systems are highlighted.

**Course Fee: \$500.00 full day
\$300.00 per half day**

Analysis & Testing



Hilton York Hotel, York, UK

November 18-22

Virtually all patient and business critical decisions made by Qualified Persons and other quality professionals are in some way made on the basis of data provided by an analytical laboratory. It is, therefore, of paramount importance that this data is accurate and can be relied upon. Hence, it is essential that these decision makers understand the basis of the analytical techniques used and their respective strengths and weaknesses.

This module seeks to provide a foundation of knowledge which will enable Qualified Persons and others to judge analytical data, ask relevant questions to aid interpretation and know when to call for additional data/advice. This knowledge is also essential when auditing laboratories.

Course Fee: £3200.00



Book your place on any of these courses, visit www.nsf-dba.com

Forthcoming Courses

What's planned for October – November 2013



Early Bird or Second Delegate discounts apply to some of our courses. Please visit our website, www.nsf-dba.com, for full details

How to Audit – Key Excipients

Manchester Marriott Victoria & Albert Hotel,
Manchester, UK

November 19-20

This course will be run by Peter Monger, a former MHRA inspector and extremely experienced auditor. He will be running this highly interactive course with the following objectives:

- Remind auditors of the key legislation and guidance around auditing excipients, GMP, IPEC, ISO 9000
- What is the role of EXCiPACT™?
- How to construct an audit plan or agenda that works
- Working through case studies and audit observations to discuss the severity ranking and references to support findings
- What to do when time on site is limited, shared or impossible

Course Fee: £1400.00



How to Audit – Chemical API Manufacture

Manchester Marriott Victoria & Albert Hotel,
Manchester, UK

November 21-22

During this course we will discuss the standards used and the industry norms applied during the audit of API manufacturers. The aim of the course is to:

- Improve your knowledge in the area of API auditing
- Improve your skills in preparing for API audits
- Increase confidence in conducting API audits
- Understand how to report observations and respond to corrective action plans

We will also develop the tools you will need such as an audit plan and aide-mémoires to cover specific areas within that audit.

Course Fee: £1400.00



Pharmaceutical Legislation Update: Continuing Professional Development for Qualified Persons & Technical Personnel



NSF-DBA Boston Office, Boston, MA, USA

November 19

Quality and technical personnel need to be informed and aware of pharmaceutical legislation. Changes in legislation and guidelines, and the interpretation of them, can have significant implications for the individual and their company. We will cover:

- USA changes to legislation and FDA guidance
- The reality and interpretation of recent and new EU legislation
- Changes to EU GMPs
- An update on ICH and other international initiatives
- UK updates

Course Fee: \$950.00

Pharmaceutical GMP

Park Hotel Amsterdam, Amsterdam, The Netherlands

November 25-28

It is a legal requirement that all staff receive regular training in Good Manufacturing Practice. This course is designed to provide you with up-to-date knowledge of new and impending GMP regulations and current 'hot topics'. This course will cover:

- Why we have GMP
- EudraLex Volume 4
- A clear comparison of EU and FDA GMP requirements
- Up-to-the-minute information on new GMP initiatives and regulations
- Practical advice on dealing with the 'difficult areas' of GMP
- An understanding of how GMP is influenced by...
- An appreciation of the critical GMP issues for...
- A panel discussion session to explore YOUR specific GMP problems

Course Fee: £2400.00



Forthcoming Courses in Italy



In Fall 2013 we will be running two of our most popular courses in Milan. These courses will be delivered in Italian; check our website www.nsf-dba.com for further details.

International Pharmaceutical Legislation Update: Continuing Professional Development for Qualified Persons & Technical Personnel

October 15

Human Error Prevention

November 28-29

Visit www.nsf-dba.com for more information on all our courses

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

Regulatory Update



EU Pharma News

Update on the Implementation of the Falsified Medicines Directive

As of July 2, 2013, the Falsified Medicines Directive (FMD Directive 2011/62/EU), requires all APIs imported into the EU to be certified as meeting EU Good Manufacturing Practices (GMPs) by a competent authority of the exporting country, unless they have been assessed by the European Commission as having been produced with acceptable regulatory controls in a location on its acceptable country list.

As of the July 2 deadline, the Commission had approved four nations for its list of acceptable countries: Switzerland, Australia, Japan and the USA. Four other countries (Brazil, Israel, New Zealand and Singapore) had applied to go onto the list. New Zealand and Brazil are currently undergoing the approval process. However, the Commission had indicated that Israel and Singapore would not be acceptable at this time and that both countries will be issuing GMP compliance certificates.

The two major exporters of APIs to the EU are India and China. As of July 2, the EC position with each was as follows:

India

The Central Drugs Standard Control Organisation (CDSCO), through the Drugs Controller General of India (DCGI), had been appointed as the competent authority to issue the certificates for API exports to Europe. In mid-June 2013, the CDSCO published an online list of certificates issued to date, with links to pdf copies of the certificates, (http://www.cdsc.nic.in/WC_scanned_copies.htm). At the time this list was first published, just 57 companies were listed, out of the estimated 400 Indian companies exporting to the EU. By July 2, the number of companies certified had risen to 173, which the Indian authorities claim represents 99 percent of exporting sites. However, this figure would appear to represent less than half of the 400+ Indian API sites identified in the EU's survey of exporting sites. The reason for the discrepancy is thought to be that some sites may be named on EU Marketing Authorizations but may no longer be active. A second reason (according to the Indian Controller General) is that sites that thought they would not pass the review did not apply.

China

The China Food and Drug Administration (CFDA) has stated that it will issue API certificates for API sites registered with the CFDA. However, this does not include all API sites exporting to the EU. At a meeting between industry trade associations and the Commission on July 4, it was reported that 14 Chinese provincial authorities have issued written confirmations and 59 API manufacturing plants have been inspected, corresponding to 188 APIs. One of the associations reported that according to internal feedback received, some critical APIs were not covered and the companies had little information as to when written confirmations would be available.

By July 2, six member states (Spain, Italy, United Kingdom, Ireland, Germany and Slovakia) had communicated to the Commission that they intended to apply the permitted waiver for sites holding a GMP certificate from an EU regulatory authority.

In mid-June, the Heads of Medicines Agencies (HMA) published guidance to industry regarding the importation of APIs, which included a flow diagram of the process that should be followed when importing APIs from outside of the EU.

Following publication of the HMA guidance, the Commission announced that it had established a business continuity plan and the European Medicines Agency (EMA) had also set up an API rapid alert reaction team in case of problems. Industry was advised to follow the flow diagram in the HMA guidance and to rapidly inform the EMA and the Commission in case of issues.

Draft Annex 16: QP Certification and Batch Release

On July 5, a draft revision to Annex 16 was published. This revision is a complete re-writing of this Annex. The reason for the revision is given as the need “to reflect the globalization of the pharmaceutical supply chains and the introduction of new quality control strategies”. Comments are due to the Commission by November 5, 2013.

The revised annex starts by making it clear that the ultimate responsibility for the performance of an authorized medicinal product over its lifetime lies with the Marketing Authorization (MA) holder. However, the responsibility for ensuring that a particular batch has been manufactured in accordance with the MA, with EU GMP and with local laws and those of the destination country lies with the Qualified Person (QP) certifying that batch as being suitable for release.

The draft makes it clear that batch release has to occur after certification by the QP, but then states that batch release “could be done by the QP as an integral part of certification or it could be done afterwards by another person. In this case, this arrangement should be delegated by the QP in a SOP or contract”. This is an important clarification as some Member States’ competent authorities have been insisting that batch release must be performed by the QP.

The ‘process of certification’ section starts by making it clear that the certification of a batch can only be performed by a QP of the Manufacturing and Importation Authorization (MIA) holder that is named in the MA as a site of manufacture for the product.

This section continues by stating “Any QP involved in the certification, or confirmation, of a batch must have detailed knowledge of the steps for which they are taking responsibility. The QPs should be able to demonstrate knowledge of the product type, production processes, technical advances and changes to GMP”. QPs must ensure they meet their obligations through an agreed quality management system.

The new text explicitly states that “If the QP is responsible for confirming compliance of those operations with the relevant MA then it is expected that the QP has access to the necessary details of the MA to facilitate declaration of compliance”. This clarification is important as QPs at contract manufacturers are not always provided with the necessary MA details by the contract giver.

The revised annex is consistent with the existing annex in that when partial manufacturing occurs within different sites within the European Economic Area (EEA), it allows QPs at each site to take responsibility for their operations providing that this is covered by a written agreement. This written agreement can be in the form of an SOP where the QPs are operating at a single MIA holder. A template for the written agreement is given as an attachment to the Annex.

Where a product is imported from outside of the EEA, the draft requirements are again essentially the same as in the current Annex 16 but the product must also either undergo the required re-testing within the EEA or be “in accordance with an approved Real Time Release Testing programme”.

This aligns the revised annex with the Committee for Medicinal Products for Human Use Note for Guidance (CHMP NfG) on Real Time Release Testing.

With regard to the sampling of imported products, the annex states that the sampling should be taken after arrival in the EEA. However, it does allow that if there is a risk that a sample would not appropriately represent the batch it may be necessary to take additional samples during processing in the third country. In this case, the samples should be shipped with and under the same conditions as the batch they represent.

The new Annex no longer contains the eight routine duties of the QP, which originally came from the UK’s Code of Practice for QPs. Instead, these are replaced by 22 operational responsibilities. The QP must personally ensure the first three of these responsibilities but may delegate the remaining 19 to appropriately trained personnel or third parties. It is recognized that the QP will need to rely on a quality management system. The QP should have ongoing assurance that this reliance is well founded.

Section 4 of the revised Annex deals with relying on GMP assessments by third parties, i.e. audits. It states that Chapter 7 of the GMP guide should be complied with and gives detailed guidance on the content of audit reports.

Section 5 deals with unplanned deviations. This section essentially reproduces the guidance contained in the 2009 Reflection Paper in that it states that the registered specifications must all be complied with, but if a deviation occurred, the finished product may still be considered to meet the requirements of the MA and GMP when these details have been taken into account:

- The deviation is unexpected, unplanned and relates to the manufacturing process and/or the analytical control methods as described in the Marketing Authorization
- An assessment has been performed using quality risk management and supports a conclusion that the occurrence does not have an adverse effect on the quality, safety or efficacy of the product
- The risk management has evaluated the need for inclusion of the affected batch(es) in the ongoing stability program
- For biological medicinal products in particular, the risk management has taken into consideration that even minor changes to the process can have an unexpected impact on safety or efficacy

Section 6 deals with batch release. Until it is released, the batch should remain at the site of manufacture or be shipped under quarantine to another authorized site. It requires safeguards to be in place to ensure that uncertified batches are not released.

This draft revision of Annex 16 represents a significant move to harmonize the expectations for the role of the QP across the EEA. It introduces the latest thinking on areas such as risk management, quality systems, supply chain controls and Real Time Release Testing.

FDA News

New Draft on Contract Manufacturing Arrangements for Drugs: Quality Agreements

On May 28, 2013, the US FDA issued the draft guidance, Contract Manufacturing Arrangements for Drugs: Quality Agreements.

This guidance appears to contain similar requirements as the EU Guidelines for

Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Chapter 7. The following products are within the scope of the guidance:

- Human and veterinary drug products
- APIs and intermediates
- Some combination products
- The drug constituents of combination drug/device products

The guide defines the who and what of contract manufacturing and emphasizes that both the manufacturer and the owner (the party that introduces or causes the introduction of a drug into interstate commerce whether or not such drug is covered by a marketing application/license) have obligations to ensure cGMP compliance.

The guidance also incorporates new requirements from the Food and Drug Administration Safety and Innovation Act (FDASIA): both owners and contracted facilities are responsible for ensuring their products are not adulterated or misbranded, which includes a revised definition of cGMP as “implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in the drug manufacturing and finished drug products (which includes excipients)”. Owners and contracted facilities are also responsible for indicating the responsibility for setting specifications for raw materials; auditing, qualifying and monitoring suppliers; as well as conducting required sampling and testing.

The guidance brings together key elements from ICH Q7, Q9 and Q10 and explains the FDA’s expectations for contract manufacturers to implement quality management practices. The guide recommends that owners and contracted facilities establish a written quality agreement that covers:

- Purpose/scope
- Terms, dispute resolution
- Responsibilities
- Change control and revisions

Within the section describing responsibilities, the draft guidance provides specific detail with regard to:

- Quality unit responsibilities (this section is the longest and most detailed)
- Facilities and equipment
- Materials management
- Product specific requirements and responsibilities
- Laboratory controls
- Documentation

Section V of the guidance provides specific examples of problems that can arise in contracted manufacturing arrangements with respect to facilities and equipment, documentation of the manufacturing process and contracted laboratory services. The FDA describes actions that may be taken against the owner and the contracted facility depending on the specifics of the issues in question. In all examples, the owner of the product is ultimately responsible for the quality of the commercial product even if it contracts out significant portions of manufacture and testing. The contract facility is responsible for complying with cGMP requirements independent of what might be specified in the Quality Agreement.

FDASIA Implementation

On July 15, the FDA announced a proposed regulation to implement an administrative detention authority with respect to drugs as authorized by amendments made to the Federal Food, Drug, and Cosmetic Act (FD&C Act) by FDASIA. When finalized, the regulation will allow the agency to better protect the integrity of the drug supply chain by allowing FDA officers to prohibit distribution of believed misbranded or adulterated drugs until the agency’s course of action is decided. The duration of administrative detention cannot exceed 30 days unless otherwise officially extended. The proposed rule also specifies:

- The content of the detention order including the reason for detention, identification of the detained drugs, time/date of the detention order and details on appeals to this detention
- How product subject to the detention order must be labeled/marked
- How to appeal the detention order
- How drugs under the order may be moved
- Other actions that may be implemented
- How the order may be terminated

Also on July 15, the FDA announced the availability of the draft guidance, Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection. This draft guidance defines, by way of example, the actions, inaction and circumstances that the FDA considers to constitute delaying, denying, or limiting inspection, or refusing to permit entry or inspection for the purposes of making a drug adulterated. The guidance provides examples of what constitutes the following actions:

- Delay of inspection for preannounced inspections, delay during an inspection and delay in producing records
- Limiting the inspection including limiting access to the facility and manufacturing process, limiting photography, limiting access to or copying of records, and limiting or preventing sample collection
- Denial of inspection
- Refusal to permit entry or inspection

NSF Health Sciences Qual

NSF Health Sciences Qualified Person (QP) training provides practical, focused, face-to-face instruction from seasoned professionals and University lecturers who are acknowledged experts in their fields.

Our founder, David Begg, began QP training in 1990 when the QP Study Guide was being developed. David saw the need to educate beyond a minimum, to give QPs and other pharmaceutical professionals a syllabus of education that truly prepares them to work in our industry. This belief in education has been maintained over 23 years and 150+ courses, and has helped over 250 professionals gain QP status. The rigorous course can be used to gain postgraduate qualifications up to the MSc level. It has also been accepted by health authorities in several EU member states as sufficient training to allow non-pharmacists to become QPs.

The course acts as continuing professional development for quality professionals from other disciplines such as auditing, manufacturing, QC and engineering, as well as for existing and prospective QPs. It provides the knowledge and practice QPs will need to face in their ever-demanding roles.

For more information on **NSF Health Sciences QP training in the EU**, visit <http://nsf-dba.com/pages/qp-training> or contact Stella Pearson-Smith in our UK office at sps@nsf-dba.com.

Whilst the legal requirements for the Qualified Person (QP) have been enshrined in EU legislation for over 30 years, several other regulatory agencies are now naming individuals for certain Quality related roles.

Despite the need for a QP not being a legal requirement in the USA, more and more firms are asking NSF Health Sciences to provide an in-house program to educate selected Quality and Technical Professionals, often globally, across their organization, to a standard similar to the EU QP. This has helped facilitate better decision making, staff development and retention of key people.

For more information on the options for **in-house Quality Professional Programs** contact Austin Caudle in our US office at acaudle@nsf.org.



The Route to QP Eligibility in the EU

In this article, James Culyer, a Supply Chain Assurance Manager at Bard Pharmaceuticals Ltd in the UK, provides an engaging personal account of his experience with NSF-DBA's QP program, from start to finish.

The route to QP eligibility starts long before you make the conscious decision to send off the application form for that first QP module training course. It even starts long before most people know what a QP is; let alone what's involved in becoming one. It actually starts when you make the decision at some point in your career that you want to work in the pharmaceutical industry. You could argue that the route starts even earlier at the point when you choose your university degree course as chemistry, microbiology, pharmacy or other life science qualification.

I feel lucky in my own particular career route leading up to realizing I wanted to be a QP. I already had experience working in a QC laboratory in a sterile manufacturing facility and in validation roles at sterile injectables, non-sterile liquids, and oral solid dosage forms manufacturing sites. That gave me a strong foundation in different manufacturing techniques and processes that was to prove invaluable to me both during the training and the viva process, and beyond in the real and chaotic world of the QP. When I finally approached the site Quality Director to discuss the possibility of becoming a QP, the decision was borne out of a strong desire for challenge – not just the challenge of the training and qualification process, but out of a desire for an ongoing career challenge. I wanted a position in the company that challenged me on a daily basis, where every day would be slightly different, and every problem complicated with a slightly different set of considerations to take into account. If you don't crave this kind of role, give up on the QP dream now!

Once the site Quality Director agreed to allow me to pursue my chosen career, I began the first module of NSF-DBA's QP program. My company had a long-standing relationship with NSF-DBA; with all seven of our site QPs having studied and qualified with them, including my manager and the Quality Director himself. The relationship spanned many years and had become a two-way process with many of our QPs routinely

ified Person Training

involved in delivering material and sharing experiences as industry presenters at NSF-DBA's many and varied training courses. There was a deep trust in the abilities of both parties to deliver exactly what was needed. The thought of going elsewhere for QP training was not even entertained. NSF-DBA was quite simply our first and only choice. From the time I applied, I had a full three weeks to mentally prepare myself before the start of the course. This involved talking to the existing site QPs and attempting to discover what on earth I had let myself in for. Many hints and tips for survival were gladly given; how to handle the revision workload, how to survive the exams, how to get the most out of the courses, which were the best clubs, bars and restaurants to go to, etc. Basically, all the essentials!

I needn't have worried; the courses themselves are extremely informative and quite simply great fun. The atmosphere is relaxed and informal, and the speakers are experts in their respective fields. From the very first morning of the first course you start the networking process, and that is just a formal way of saying you start making new friends. As you progress through the modules, you start to realize how important, and in fact essential, these new friends really are. They allow you to access a vast amount of industry experience and knowledge, provide the opportunity to visit and understand other manufacturing sites and review quality management systems, and give you the support of a large number of like-minded people who are going through exactly the same process. The huge emphasis on networking is one of the best things about the NSF-DBA approach to QP development. Practically every aspect of the course – the training techniques, the venues and the extracurricular activities – is based around encouraging you to build a broad and long-lasting network of contacts that will serve you both through the viva process and beyond throughout the rest of your career.

The other great thing about the NSF-DBA QP courses is the personal tutor system. Once you sign up for a certain number of the QP modules¹, you are assigned a personal tutor. This will be one of the NSF-DBA team members actively involved in the QP training courses, who will inevitably have acted as a QP at some point in his or her career. You meet with your assigned personal tutor during each module and spend a short period of time reviewing your progress and your next steps toward the viva process.

Additionally, you can email or phone your personal tutor any time in between those meetings to ask for advice and guidance. Your tutor acts as an expert mentor for the QP qualification process, helping you identify your strengths and weaknesses, defining development needs and even providing opportunities or contacts within the industry to address those needs. This support becomes ever more important as you progress through the QP modules and start to complete your viva application form, which in itself serves as a gap analysis of your eligibility to act as a QP. The tutor remains an ever-present source of information and guidance right up to the point you sit, and hopefully pass, your viva.

In the months leading up to the viva process, NSF-DBA offers one further service (free of charge), the mock viva. It takes place at the NSF-DBA offices in Kirkbymoorside² and serves as an invaluable preparedness check prior to submitting your application form. The extremely intense three- to three-and-a-half-hour session serves to identify the gaps you have that need filling, your ability to handle a very realistically simulated viva experience, and the overall manner in which you present yourself and approach the various different types of viva questions and scenarios. I remember my own mock viva very well, and remember how helpful it was in focusing my revision topics leading up to the real thing a few short weeks later. All credit goes to my own two mock viva assessors, Mike Halliday and Peter Smith, who did an excellent job in the preparation for the day and in the execution of the process itself.

Overall, I don't think you can go wrong, or do better, than to choose NSF-DBA as the training provider for the QP program. The focus is 100 percent on getting you through, successfully, first time. The structure of the courses and course material, the social aspects of the modules, the emphasis on networking, the tutoring and mentoring, and the overall supportive nature of the service they provide give you the best chance possible.

After you finish the course, QP Alumni meetings are available to keep you up-to-date (meetings count towards CPD) and give you an opportunity to reminisce with fellow students.

¹ Attendance at four QP modules is required to become a 'core' QP delegate. For details of the benefits, please contact our QP Administrator, Stella Pearson-Smith, sps@nsf-dba.com

² Other locations available by arrangement

NSF-DBA, NSF-Pharmalytica and Becker & Associates are changing their names to **NSF Health Sciences** on January 1, 2014.



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