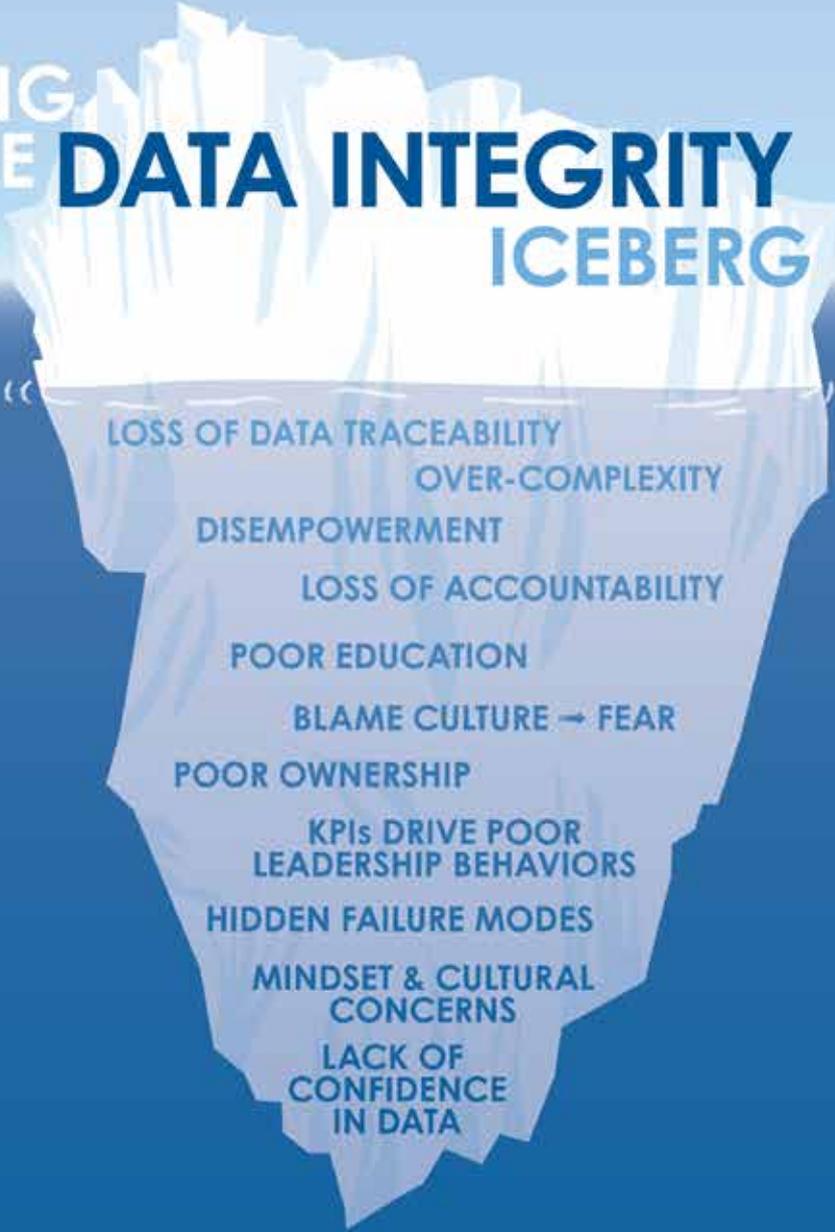


Journal

2015, Issue 32

The right people. The right solution. The first time.™

AVOIDING THE DATA INTEGRITY ICEBERG



LOSS OF DATA TRACEABILITY
OVER-COMPLEXITY
DISEMPOWERMENT
LOSS OF ACCOUNTABILITY
POOR EDUCATION
BLAME CULTURE → FEAR
POOR OWNERSHIP
KPIs DRIVE POOR
LEADERSHIP BEHAVIORS
HIDDEN FAILURE MODES
MINDSET & CULTURAL
CONCERNS
LACK OF
CONFIDENCE
IN DATA



Health Sciences
Pharma Biotech
Consulting

Formerly NSF-DBA

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welcome

Data Integrity – Are you at risk?

During a recent audit I was reviewing a batch record that seemed odd. The signatures and dates just didn't match up. Cutting a long story short, operators routinely completed the batch record many hours after the event. They knew this wasn't right but they had little choice. The size and complexity of the record had increased alongside cuts in staff numbers. And yes, they had flagged up the problem with management who did nothing. This is just one example of good intentions that can lead to bad data. This edition of *The Journal* includes a review of the contributing factors that can lead to data integrity issues that can have catastrophic consequences. Are you at risk? Just answer the following questions:

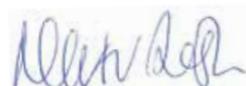
- > Are your processes and procedures really simple?
- > Do leaders and supervisors visit the production lines daily?
- > Do they stop to actively listen to operators concerns and act quickly?
- > Are deviations and mistakes seen as learning opportunities?
- > Do you have an engrained open, transparent and blame-free culture?
- > Is there shop-floor ownership of quality?
- > Is everyone focused on the patient?

If you have answered yes to all of the above, congratulations. You probably won't have any data integrity issues. As an aside, would your approved suppliers and manufacturing partners answer likewise? If you have a few *no's* then please read on. You may be at risk. You may also benefit from attending our new course, *How to Audit for Data Integrity*, on June 1 in Manchester, UK.

Auditing for data integrity requires a different, more challenging, approach. The course covers what to look for as evidence of data integrity problems during either specific QC laboratory audits or general GMP audits, including how to check data for evidence of fraudulent manipulation and how to distinguish between genuine errors and fraudulent behavior.

We may all have the best intentions to do the "right thing" at the right time, but does your GMP data prove this best intention is achieved in practice, in the laboratory or on the shop-floor?

Enjoy the read and keep in touch!



Martin Lush



Tech Talk

Continued/Ongoing Process Verification

The 2011 FDA Guidance on Process Validation and the recently issued revision of EU GMP Annex 15 require that manufacturers monitor performance of their processes throughout the commercial life of the product. The FDA calls stage 3 of its process validation "continued process verification," described as "An ongoing program to collect and analyze product and process data that relate to product quality..." The revised EU Annex 15 uses the ICH Q8 terminology of "continuous process verification" to describe the PAT approach to in-process monitoring during manufacture, and consequently calls the validation step analogous to stage 3 of the FDA guidance "ongoing process verification." While it is unfortunate that the language used by FDA and EMA is different, even confusing, the concepts are identical.

Some definitions:

- > The FDA process validation guidance states that "The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal."
- > The revised EU GMP Annex 15 states "Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated."

What does it all mean?

- > While the concept of continued/ ongoing monitoring of a manufacturing process may be new to many in the pharmaceutical industry, it is virtually universal in other manufacturing sectors. It is sad that the science-led pharmaceutical industry has to be driven to do what is in its own best interest by regulatory guidance. Fortunately, thanks to others, the tools and techniques that are required are very well established and understood and are usually referred to as statistical process control (SPC) tools.



by Pete Gough,
Executive Director, NSF Health Sciences Pharma Biotech Consulting

40 years' experience in pharmaceutical law, manufacturing, QC and quality systems. Now helping our partners understand ever-changing regulatory expectations to remain compliant.



Tech Talk

Words of Wisdom

The logic of validation allows us to move between the two limits of dogmatism and skepticism.”

Paul Ricoeur

- > Both FDA and EMA refer to the use of SPC tools. The FDA recommends “... that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability.” Similarly, the revised EMA guidance states that “Statistical tools should be used, where appropriate, to support any conclusions with regard to the variability and capability of a given process and ensure a state of control.”
- > The three main SPC tools used for continued/ongoing process verification are control charts and process capability analysis to monitor release test parameters, and linear regression to monitor stability trends.

The concept – why bother?

The concept behind continued/ongoing process verification as part of overall validation of a process is simple: You first establish a baseline of what is normal variability for a given process and then use the SPC tools to alert you to any significant departure from that baseline. A validated process should only have “common cause” variation (often colloquially called random variation) operating; it is then said to be in control. Departures from the baseline often occur when something changes introducing a “special cause.”

Control charts provide an alert when a potential special cause enters a system. The related tool of process capability analysis compares the normal variability of a process to the specification limits to provide a measure of the probability of the process consistently meeting the specification. The tool that is employed to assess the rate of change of a specification parameter during a stability study is linear regression, as defined in ICH Q1E. For a process to be considered to be operating in a validated state it has to be in control and capable, and the stability profile should not be changing.

Today the calculations necessary to use these SPC tools are easily accomplished using one of the numerous software packages available. This also has the advantage of eliminating the all too frequent calculation errors that occurred when the calculations were performed manually.

Conclusions and Recommendations

So continued/ongoing process verification is now a regulatory expectation, for both EU and US markets. Companies must have effective systems to capture the necessary data and perform the appropriate statistical analysis. Most companies who do this find that they generate valuable information that not only ensures that they comply with regulatory expectations but also allows them to improve their processes and reduce costs.

If you do not already have continued/ongoing process verification established as an integral part of the validation component of your quality system, then you need to take action now. The following courses will help you understand what you need to do:

- > **Modern Approaches to Process Validation** in Manchester, UK, June 16-18, 2015, will explain the concepts defining the process validation requirements of the FDA and the revised EU Annex 15
- > **Mathematics & Statistics** in York, UK, September 14-17, 2015, will cover the detail of the SPC and other statistical tools and how to use them

NSF's Quality Certification Education Program is World Class

Medicines are as good as the people making them –
So investing in your staff helps make better medicines

Most of you will already know that we are Europe's leading provider of education for Qualified Persons (QPs). Hundreds of QPs, key industry leaders and inspectors are included in our QP alumni. Many describe our program as "life-changing," and "deeply fulfilling."

What surprises many is that we also educate people in our QP syllabus outside the EU via our Quality Certification Program (QCP). These courses are based on our QP study requirements and are tailored to the local regulatory environment and audience.

The modules provide the knowledge and skills required of the quality leader whether this person is in quality, manufacturing, R&D or another support function. Companies preparing for success in a very unpredictable world know it depends, almost entirely, on the knowledge, skills and competencies of its people. Our QCP provides our clients with a workforce with a detailed understanding of:

- > The regulatory requirements – not just what, but the why
- > How medicines work and the product attributes that impact on safety, quality and efficacy
- > Manufacturing processes – how to design, validate, manage and maintain
- > The product life cycle – what happens from start to finish
- > The essence of the GMP requirements for every dosage form
- > Quality management systems that drive continuous improvements as well as protect patients

In addition, participants who have attended one of our in-house Quality Certification Programs leave with:

- > Leadership, communication and interpersonal skills second-to-none
- > The ability to solve problems quickly

- > What it takes to make the right risk-based decisions
- > A passion for doing the right thing, no matter what, by leading by example

Example of Success

One client partnered with us to deliver QCP education across their organization. Key technical and quality supervisors and leaders were all involved. All listening to same message. All leaving with the same knowledge, skills and commitment. They have been so pleased with the return on investment they have successfully completed three series, each of five modules. We are now helping them develop in-house subject matter experts, decision makers and trainers tasked with taking the program across the global organization.

Successful Remediation and QCP Education Go Hand in Hand

Companies facing severe regulatory censure fall into two categories. Those who want a quick fix and those who want to emerge stronger, more competitive and better prepared for the future. Our Quality Certification Program has helped the latter to achieve these goals.

Key Messages

- > To survive and prosper you must have people with in-depth skills and knowledge, and the ability to use both
- > Our customized Quality Certification Program has helped transform our clients' quality culture in the EU, Canada, US, India, China, Singapore and Australia
- > Don't get left behind. Help to protect your business. Investing in a customized Quality Certification Program has a return on investment that has transformed a company's growth/survival opportunities



by Mike Halliday,
Executive
Director, NSF
Health Sciences
Pharma Biotech
Consulting

Responsible for our world class QP and IRCA education programs. With his unique training style and 35+ years' experience Mike is passionate about helping you get the most from your people.



For more information contact Mike Halliday, Executive Director mikehalliday@nsf.org

Getting to the Bottom of Data Integrity

Understanding the Thinking That Drives the Behavior

Many years ago I had the pleasure of being audited by Dr Ronald Tetzlaf, one of the most systematic, organized and methodical FDA investigators I've ever met. He could find problems you didn't even know you had. Ron reputedly said "If it's not documented, it hasn't been done." Well, reading about the data integrity issues exposed by regulators, it seems that even if it has been documented, you can never be sure! Before we go any further, let's get a few things straight...

Firstly, data integrity is a global issue and not restricted to one particular marketplace or region of the world. It is also not new. Problems with data integrity have been around for years. Secondly, data integrity problems are not restricted to the QC labs.

DATA INTEGRITY: ARE YOU AT RISK?

Just answer the following questions to see if your ship is heading toward the "data integrity iceberg." Get together with your colleagues and answer *yes* or *no* – don't do this in isolation!

- > Have you seen data that is just too good to be true?
- > Are your batch records or QC records pristine and beautifully presented?
- > Do you consider deviations, OOSs and the like to be an inconvenience or just plain bad news?
- > Are you focused on driving down deviation incidents?
- > Is the root cause of many of your deviations so called human error?
- > Do you have a blame culture? Ask people on the shop floor before you answer this!
- > Do you train your people to push the right buttons, without explaining the why?
- > Do you blame people for mistakes, rather than focusing on the systems and procedures?
- > Are your systems and procedures overly complex?
- > Is your company's primary focus to get product out of the door no matter what?

If you have too many yes's, start taking action now – you are on course for a data integrity problem.

We help a lot of companies permanently resolve their data integrity problems by first understanding the root causes for the behaviors that drive the actions. Only when you understand the "why" can you make a difference. In our experience very few people are truly malicious in their intent. OK, there are always, thankfully very rare exceptions but most people go to work to do the best they can, with the knowledge they have and the tools (the systems, procedures and practices) at their disposal. Let's start with a few examples:

Company A: Each 25 kg container of API had to be identified using NIR. The only problem was that the NIR test station was on the other side of the warehouse. So, instead of testing all 250 containers and moving 6,250 kg (my back is already twinging), samplers devised a cunning plan. They took all 250 samples from one container instead. Although they had been trained on how to take samples, they were not empowered and had not been educated as to the reasons why and, in particular, the impact on product quality and patient safety. Whether the samples were representative or not didn't even enter their minds. Now, you may be shaking your heads in disbelief, but

you can understand where the samplers were coming from. The solution? Better education, and investment in a portable NIR scanner. NOT adding additional checks, additional procedures or worse still, disciplining those involved. You must do all you can to avoid driving problems underground.

Company B: During completion of a batch record, a page containing raw data was replaced. The original contained multiple errors and looked, in the words of the operator, "embarrassing, untidy, and shameful." All the data was transcribed accurately, just without the multiple corrections and supporting signatures and dates. Most of you will be shaking your heads (even more vigorously this time), thinking signed and dated corrections are fine. Well, not in this "saving face" culture where overbearing hierarchy, deference to authority and poor education as to the "why" led to a very different behavior. The solution? Not so simple this time, so please read on!

DATA INTEGRITY: WHAT DOES IT MEAN ANYWAY?

Most people care about what they do. When they understand the "why" and they are risk-aware, then they really understand the impact of getting it wrong on patients and end users. The term data integrity, or DI, suggests a basic accuracy or authenticity concern when in fact that is the symptom, not the cause. The true root cause of DI issues lies with education and the culture of supervision and management.

I sat through a client's DI training session the other month that emphasized "its vital importance for compliance and license protection", and how data integrity was an "essential part of Good Manufacturing Practice." I'm sure everyone left the room as disengaged from DI as when they entered. I doubt if behaviors changed. Contrast this with another

client, who, with our input, took a very different and more personal approach. "Data integrity" didn't even appear in the session title. This highly interactive session entitled *Personal Integrity: Telling the truth and nothing but*, addressed:

- > How the medicines they manufactured worked and the difference each made to the quality of life of their patients
 - > The trust patients place in each and every one of them... to get it right every time
 - > The complete product lifecycle from research to commercialization. Who did what and why, and where specifications and procedures originated from
 - > How manufacturing and marketing licenses (their licenses to operate) are granted based on DATA and TRUST
 - > How regulatory inspectors assessed the company's competency to operate based on the data they review, what they observe and TRUST
 - > What can go wrong when the data trail (story line) is either corrupted or lost and how this also erodes regulatory TRUST, which then takes years to rebuild
 - > Personal accountability for making sure the data recorded is factually accurate and tells the whole truth and nothing but the truth
 - > How QA relies on data to release each batch; inaccurate data can lead to wrong decision making
 - > Practical examples of what could go wrong if data was inaccurate or unreliable, always linking back to patient impact
 - > That data integrity is about the documentation and the data telling the story of the what, who, how, where and what if
- Participants were provided with a fictitious batch record with errors and mistakes and given 30 minutes to find them and come to a decision. Release to market or not?



by Martin Lush,
President, NSF
Health Sciences
Pharma Biotech
Consulting

Over 35 years' experience in operations, QA, troubleshooting and due diligence. Now committed to helping clients do better with less.

Words of Wisdom

So ensuring the integrity of the data and integrity and validity of the connection is a very important element in any company's strategy ”

John Wendell
Thompson,
Chairman
of Microsoft
Corporation

Continued **Getting to the Bottom of Data Integrity**

Words of Wisdom

You can have data without information, but you cannot have information without data.

Daniel Keys Moran

The most memorable part of the session was the 15-minute wrap-up by a member of the leadership team who emphasized that “we are only as good as our data” and that “everyone is accountable for its accuracy.” One point struck a chord with me: “Whenever you record or sign anything, just tell yourself that, by doing so, you are releasing the batch. You are each accountable.” She also said that leadership was responsible for “providing the systems, education and culture to ensure this happens every single day.”

Key messages:

- > The term data integrity hardly does it justice. If you want people to really get it, make it personal, emotional, meaningful. If they don’t see the “what’s in it for me” and feel connected, why should they bother? It’s not about compliance, it’s about the patient
- > Always check that your culture, systems and practices drive the right behaviors. Use anonymous surveys, walk the floor – anything that gets you to the truth
- > Train your auditors in how to detect the real causes of data integrity issues, most of which are behavioral, not technical

GETTING TO THE BOTTOM OF DATA INTEGRITY: FOUR TO EXPLORE

In our experience data integrity is usually the tip of a very big iceberg. Beneath the surface can be a number of contributing factors, rarely just one. These are mostly behavioral, not technical. If you don’t want your business to be sunk by DI you have to fix what lies beneath the surface. So, in no order of priority, here are four major contributing factors:

1. Ignorance and disengagement

As the old saying goes, ignorance breeds contempt. When people don’t understand the “why” and the importance of what they do, they are more likely to just “check the box,” no matter what.

Key Messages:

- > Make sure your training sessions provide context and the reasons behind the rules. Explain the potential consequences to the company and its patients when DI is not maintained. If you can’t make these personal, emotional and relevant, you’ve failed
- > Education alone won’t work. The job of leadership is to create the culture to make it work. The job of shop floor supervision is to maintain high levels of engagement to keep the check box mentality at bay. If your supervisors and first line managers are not visible, approachable and proven educators, don’t be surprised if the team switches off

2. Problems are bad, leading to FEAR

For those of you who have attended our courses on Human Error Prevention and Deviation and CAPA Effectiveness, you already know our philosophy on problems, out of specifications and other such unplanned events. You will have heard our course tutors say, “Problems are great, the more the better,” “The more problems you have, the greater your chance of success” and “You learn more from your problems and failures.” But this is only true if:

- > You have an open and blame-free culture, one that encourages people to raise their hands when they make a mistake without fear of personal consequences
- > You have key performance indicators that drive the right behaviors rather than encouraging people to reduce deviation incidents. You actually want people to raise more because you can’t fix problems you don’t see
- > The incident investigation always focuses on the process, not the person
- > The actions taken concentrate on prevention of a recurring issue, not quick fixes

Contrast this with an alternative. I was curious about how a client improved its measure on “document right first time” from 70 to 95 percent with no apparent action taken to simplify or redesign the batch records. The reason for the improvement appeared obvious when I noticed that management had introduced a “three strikes and you’re out” policy. On your third consecutive document error, you got fired. Of course, this drove human nature to seek ways of producing perfect documents regardless of the need for authenticity of entries, accuracy and timeliness. So, instead of looking for the real reasons for poor completion of batch records, management created a culture of fear that led to data integrity issues and, ultimately, risk to patients.

It’s worth mentioning the impact of national culture here. It’s a simple fact that in certain “saving face” cultures, notably in India and China, making a mistake can feel extremely uncomfortable. We may expect our colleagues

to acknowledge their failures in front of their peers and bosses in public, but that’s asking a lot. Asking an organization to identify and seek continuous improvement, despite a historic prevailing local culture that often does not accept defaulting situations easily, is not at all straightforward. It requires a nurtured, long-term strategy that hardwires GMP into the organization’s culture.

Key Messages:

- > When you have a culture of openness and transparency, you are well on the way to fewer DI issues. Providing that is, you always use mistakes and problems as a catalyst for continuous improvement. Remember, focus on the problem (not the person) and on performance improvement (not punishment)
- > Make sure your KPIs drive the right behavior and that your leadership, at every level, creates the **see it, say it, solve it** culture. If performance data is too good to be true, it probably is. Very low levels of deviations and OOSs? Zero counts from an old, low temperature purified water system? No calibration failures? Perfect environmental monitoring data, always? Start digging. Focus on the culture, leadership and KPIs first. Be curious and be challenging, even when the data looks good

3. Over-complexity, systems no longer fit for purpose and the danger of the well intentioned shortcuts

I can remember looking through a 420-page batch record impressed by how neat and aligned all the signatures were. There were precisely 175 signatures for each batch record. I counted them. Alarming, every page was pure white. Not a mark, stain or blemish anywhere to be seen. As an ex-production guy, I knew this was just too good to be true so I started to dig, looking at the signatures. The who, when and where. I eventually found one operator who managed to be in four



Continued **Getting to the Bottom of Data Integrity**

different rooms all at the same time. Because of the complexity of the batch record and the excessive number of check signatures required, it was physically impossible for the manufacturing team to make the product and fill in the batch record at the same time. That task was done over a cup of coffee during break time!

Here's another example of "too good to be true." While looking at final yield trends it was evident the liquid filling line was losing product somewhere, yet all in-process checks for fill weight were perfect. I went to the filling room and within seconds understood why. The batch record was on a table toward the back of the room, some 10 meters away. The operators couldn't operate the line and complete the IPC check list at the same time, so they just recorded the target weight. Why didn't they flag this? Fear of raising a problem, and a fear of flagging a need for change. Operator ownership, engagement and empowerment were also lacking.



Key Messages:

- > High levels of complexity increase the likelihood of data integrity problems. Win your war on complexity and you are a long way toward reducing your risk
- > If you want to start somewhere, focus on simplifying SOPs. In our experience most are overcomplicated, poorly designed and unworkable. So many production lines and labs rely on well intentioned shortcuts just to get the job done. SOPs written without user input will fail
- > Adding additional check signatures is not the answer. This creates a false sense of security and dilutes that all important accountability
- > Sign up for our free webinar in June: *The art and science of simplification – how to win your war on complexity*. Go to <http://tinyurl.com/JuneFreeWebinar> to sign up

4. The Human Element – cognitive, psychological and physiological factors

People do the best they can with what they have. Even the most diligent staff makes mistakes that can easily be interpreted as a data integrity problem. Stress, fatigue and distraction are three contributing factors to making a mistake. Once again, your leadership skills are crucial in creating a culture that promotes accuracy and authenticity.

DI problems are a product of conscious as well as subconscious behaviors. Since 45 percent of decisions are habitual (subconscious), we really need to work hard to understand them. Remember, behaviors are a consequence of:

- > Our culture and our upbringing
- > Our education and training
- > The actions of our peers
- > The equipment, systems and procedures we have to use
- > Leadership behaviors at every level

If you're serious about reducing your risk of data integrity issues, you simply must understand the behaviors first. Address your "Four to Explore" and you will be well on your way to reducing data errors and data integrity risks.

MHRA Good manufacturing practice: data integrity definitions and guidance.

MHRA will soon be publishing an article emphasizing the importance of the right organizational behavior in preventing data integrity problems. MHRA has also published an updated version of its guidance document, *Good manufacturing practice: data integrity definitions and guidance* with some minor additions following stakeholder input. Go to the MHRA website (<https://www.gov.uk/government/publications/good-manufacturing-practice-data-integrity-definitions>) for the latest information.

For more information, please contact: EU Peter Gough (petergough@nsf.org) or Martin Lush (martinlush@nsf.org), US Maxine Fritz (mfritz@nsf.org) or George Toscano (gtoscano@nsf.org)

Additional Resources:

Protect your business from the "Data Integrity Iceberg", utilizing:



Our highly interactive program, **How to Audit – Data Integrity** will provide you with invaluable tools and techniques to help find and prevent data integrity problems.



Our on-site and residential training programs on **Human Error Prevention** will provide invaluable guidance on human error, its causes and prevention.



Get inspired and in the know by registering for our free webinars.



We provide very comprehensive, customized on-site education in each of the areas mentioned in this article.



Our consultancy support on data integrity is second-to-none. We will help you to identify and remove the contributing factors that lead to data integrity problems.

Words of Wisdom

To write it, it took three months; to conceive it three minutes; to collect the data in it all my life.

F. Scott Fitzgerald

Suffering From Molds?



by Martin Lush, President,
NSF Health Sciences
Pharma Biotech Consulting

Fact File

- > Molds are the second most common contaminant of controlled environments. Although for some of you, they are probably the first!
- > Primary sources of mold contamination can be many and varied. Vegetation, soil, paper, wood, cardboard and exposed pipework lagging or insulation can all act as contamination sources
- > Molds can produce thousands of individual spores. Although less resistant than their bacterial counterparts, these spores make it easy for contamination to spread fast, either by direct contact with surfaces or via people
- > Most don't need a lot of food and water to survive

What Must You Do When You Find Them?

Make sure you get as much data and information as possible. Without really understanding the problem, you can't deal with it. Additional cleaning will not work in isolation. Questions you want answers to will include:

- > Is it an isolated occurrence or is there an adverse trend relating to:
 - Sample location (room, corridor)?
 - Sample type (settle plate, active air, and surface or personnel samples)?
 - Type of mold isolated?
 - Time of year. There are lots more spores in the general environment during harvesting of crops and in areas of high humidity. This can lead to contaminants getting into your controlled environments via people and/or material transfer
- > What is the general level of control like for your classified areas? Good or not so good?

- Bacterial isolates?
- Non-viable particulates?
- Temperature and relative humidity?
- Differential pressure alarms and excursions?
- Air change rates/room recovery rates?
- Air flow patterns?
- > What has changed? When adverse trends are experienced something has changed. You just need to find out what and when. Look at your change control log and, more importantly, talk to the people who really know, like the operators and engineers. Poor environmental control is the symptom, not the cause, so start digging:
 - Have you changed anything to do with the HVAC system that will compromise room clean-up (removal of environmental contaminants)?



- Have you done any building work recently...or even had a plant shutdown?
- Any major engineering interventions?
- Any new operators who have inadequate or variable aseptic and gowning techniques?
- Any increase in production output which could compromise good aseptic practice?
- Changes to sanitization agents, frequency or methods?
- > Organize the data and information so you can understand it! Investigations

- of this type, when done well, generate a great deal of information and data. Make sure you create a simple and visual way to present the information to prevent confusion. For example:
 - Use cusum trends to find out when the adverse trend started
 - Mark positive locations on the facility map or schematic. Any pattern?
 - Create a timeline of events
- > Remember poor environmental control is usually due to multiple factors, some of which could be months old. Go back at least six to eight months and start linking events together.

Mold Contamination: Your Call to Action

- > Make routine plant inspections (at least weekly). Confirm all surfaces are intact and cleanable and that standards of GMP remain high. The higher these standards are, the better the environmental control. Spot potential contamination sources and remove them
 - > If you're unsure of the contamination source(s), attempt to re-establish control by doing a deep clean of the facility with a suitable sanitizing agent and sporicide. Remember, not all are equally effective against molds
 - > Work hard to establish what has changed (remember everything happens for a reason). Adverse trends are usually due to multiple causes (changes), not just one singular event
 - > Remember that good environmental control requires continuous vigilance 24/7. It's a war, not a battle
- Get better educated. To defeat molds and bacteria, you need to better understand them. We can provide you with customized on-site training courses like Contamination Control, Pharmaceutical Microbiology or Microbiological Risk Assessment and Decision Making. Our experts are some of the best in the business... and they could save you a fortune. After all, poor environmental control is always a distraction and can be very costly.

For more information on our training services, visit: www.nsf.org/training-education/training-pharma-biotech/



John Johnson, NSF Health Sciences Executive Director, responds to questions from the **Ask John** series.

Expert Corner

Invest and Prosper

John Johnson continues to answer questions from our colleagues in the pharma biotech industry and concludes, **“Well placed investments can return a dividend far greater than what was expected when you combine that decision with an investment in staff coaching.”**

After a global economic slump that has officially lasted now, at least in Europe, for seven years, experts say that society as a whole will never be the same again. Society has had to become more aware of the fragility of the economy, more aware of the consequences of poor risk-taking and more knowledgeable and circumspect about where it places its assets, savings or investments. This of course translates into our own personal choices and is reflected also in the way decisions are made in the pharma industry.

Long gone are the days when industry's leaders and decision makers could afford to be speculative in where they spent their budgets or expansive in setting headcount for the coming year. It seems a distant memory to when firms spent millions of local currency on new security or reception buildings, measured its success by its headcount or had training budgets that were the size of the GNP of a small African country.

Within society and the industry as a whole, we are now driven to gain a healthy return on any spend. There's nothing ground-breaking about that, but it has led the industry to be:

- > Keen to seek the true deliverables for any project or assignment and to define them up front of any investment
- > Laser-focused on the planning of any assignment, making sure each moving part of the program works together seamlessly
- > Aggressive in seeking the best fit option, and when using outside specialist assistance to ensure that:
 - The support can demonstrate that it is world-class in planning and execution

- The assignment is tailored to fix the problem, not just using a cookie cutter approach
- Each team member is proven to be a problem solver and an educator (to gain maximum long-term influence on the associated employees)
- Each project is carefully budgeted, deliverables measured and a detailed effectiveness check put in place

None of us now have the time, money or indeed patience for false starts, scope creep, budget defaults and reworked projects. No company has a budget or strategy for repeated recalls or regulatory action or warning letters.

Given the truism that the biggest ongoing cost that you have in your organization is **your people** and their precious time, how do firms gain a competitive advantage and build a long-term sustainable growth agenda? Ask yourself these **“Five to Thrive:”**

Key Questions:

1. Do you know the cost of GMP defaults and non-right first time in local currency? Y/N
2. Do you set local annual objectives that invest in people to deliver a costed return on investment? Y/N
3. Do you take the time to engage your finance director in your quality objectives? Y/N
4. For every process that involves more than one person, have you generated a costed flow chart that seeks to identify the common causes of waste? Y/N
5. Have you invested 70:20:10 in the design, control and monitoring of your most

complex processes, focusing heavily on designing out the common causes of error and waste? Y/N

If any of these answers are No or Don't Know, you may be unwittingly losing cash and wasting time when that cash and time could be usefully deployed on the hundred other priorities that you never get around to doing!

This leads nicely into two questions posed for Expert Corner this month.

“All my Finance Department does is peck my head on cost. They don't appreciate the legal obligations that we have in pharma and just want me to slash budgets. We've now stopped talking as we just don't seem to live in the same world. Help!”

Our proven approach to issues like this always centers on five basic themes:

- > Speak the language that gains engagement; speak in cash, time and consequences
- > Ensure all parties can see “what is in it for me”
- > Ensure everyone can gain some benefit from investing their whole selves in the project
- > Ensure you celebrate and publicize success
- > Be laser-focused on what is to be invested and what must be achieved

In this case, it is crucial to seek advice from Finance but they can't advise unless they are coached on what the regulatory rules of the game are, ie what is mandatory as GMP defines it and what is optional. All parties need to realize the consequences of poor decision making and the actual cost of GMP deviations, OOS investigations, supplier outsourcing and remote GMP oversight. Everyone needs to see the cost of additional QC sampling or testing, the cost of auditing and qualifying new suppliers as well as the astronomical costs of reprocessing, rework, re-inspection, GMP inspection failures and remediation. Does your firm actually measure the cost of a lost shift, a week downtime or a suspension in manufacturing of a week or a month?

If Finance (and the organization as a whole) knew these costs and consequences, would they make different decisions on what to

slash and what to invest? Isn't business about making a profit not just this month, but for all foreseeable months in the future? Aren't annual targets hit by a cumulative, measured achievement to a known and predictable line of sight? Remember that short-termism got the world economy into the mess it is in and it certainly won't work in turning it around.

Investing in a program to measure the **cost of poor quality**, and eliminating the known sources of waste, is critical to gain and keep that competitive edge.

But it can't be done without Operations, Quality and Finance working together as partners and custodians of the business.

Our second question is somewhat related:

“We have done what we can to drive down low-level GMP deviations but our margins haven't improved and we are still barely hitting the financial targets on each batch. What should we look at next?”

This brings to mind a recent GMP remediation project that I ran where the client had got into real difficulty during a regulatory inspection. The GMP deficiencies were serious and systemic, set into multiple processes and across several departments. At the time of the inspection, the company had:

- >60 GMP deviation reports open beyond their target completion dates
- >150 CAPA open beyond their target completion dates
- >10 periodic quality reports unfinished
- >40 complaint investigations open beyond six months
- No idea of the status of its change control requests
- Over 200 regulatory commitments ongoing

All available resource was stretched to the limit, “chasing its tail” day after day dealing with the defaulting situations.

Following a remediation methodology and short interval control, all of the defaulting actions were brought back into compliance within eight months. This was remarkable in itself (and was recognized as such by the regulator), but what made it stand out is that

Continued

Expert Corner

the culture of the company was also tackled at the same time. Small yet significant changes were made to how the team thought about its work, interacted with each other, respected each other and worked out a war on waste. A cultural sea-change can typically take three to five years yet being intuitive to the needs of the business and specific in the battles needed to be won, changes to approach can be expected within six to 12 months.

However, specific to this question, the key fact was that the company now realized that:

- > Failure to follow GMP was an operational cost to the business
- > GMP compliance actually saved the company money as defaults are an “on cost”
- > Staff used to chasing historic defaulting actions now had time to fix other issues, work on future improvement or **were just able to go home on time and spend time with their families**

Some other interesting facts:

- > A lack of visibility in tracking GMP defaults meant that ~20 percent of the QA staff were engaged in mopping up late commitments or hastily closing old investigations. **If freed up, what could you do with 20 percent more QA resources in your organization?**
- > Forty percent of critical or major deviations had happened previously yet the company had spent thousands of hours on CAPA. This CAPA had clearly been ineffective. On review, the skills and application of root

cause analysis tools were woeful, meaning CAPA was badly defined and wasn't ever going to prevent recurrence. To be sure of prevention, the root causes have to be established thoroughly. Without prevention, the future will only be a repeat of the past and this is costly

- > On analysis, each GMP deviation would cost ~£4000 in samples, tests, meetings, report writing and CAPA. Each SOP change (effective or mostly not) cost ~£2000. Some SOPs were being changed five times in a year and over 500 SOPs were changed each year! And amazingly, the amount of time the operators or end users put to SOP upgrades was less than 10 percent of the total, leading to a lack of ownership, and lack of accuracy and error-proofing
- > Investing in coaching and new systems for the following key areas led to a return to GMP compliance that everyone can take pride in:
 - Risk-based decision making for all key staff
 - Human error reduction
 - Data integrity and assurance of documentation accuracy
 - Deviation management and root cause analysis
 - CAPA definition, execution, tracking and effectiveness checks

And now within 16 months, that company has returned to health both in terms of GMP compliance and in controlling its costs.

If you are touched by these issues, please get in touch with me at johnjohnson@nsf.org

We can help. We have an expert cadre of people who have walked in your shoes, made the breakthrough changes needed and developed the tools that deliver a long-term, relatively painless business. We want you to maintain GMP compliance, reduce business-threatening risks and gain a return on investment.

Look out for our offerings in auditing, consultancy, remediation and training; and watch out for our ground-breaking two-day training course in **November 2015** on **Cost of Poor Quality**.

Contact us to help you in your **war on waste**.



Please send in your questions to Ask John at johnjohnson@nsf.org and he will answer them directly or in the next Journal.

Want to Sleep Easy at Night? Make Sure You Have Skilled and Competent Auditors!



A good audit is like a medical examination. You should come away from both with an understanding

of how fit and healthy you are and where you have to make improvements. Our unique and independently accredited **Pharmaceutical Quality Management System (PQMS) Auditor/Lead Auditor course** continues to go from strength to strength in providing companies with auditors they can trust. Auditors with the technical and interpersonal skills needed to do value-adding, risk-based audits.

Since 2011, over 540 enthusiastic, highly motivated auditors have attended our PQMS Lead Auditor course. This exceptionally successful program (both at our site and yours) runs throughout the year. In-house courses have been presented at clients' facilities in the UK, USA, mainland EU, China and Australia, all motivated to achieve the same thing:

- > To significantly enhance the skills of their auditors to help them fulfil the requirements of their demanding job, in full
- > To help ensure a common understanding and interpretation of GMP standards so that outcomes are consistent, pragmatic and science-based
- > To have the skills needed to make sure audits are value-adding and drive continuous improvement
- > To help their companies keep pace with changes in regulations and best-in-class practices across the supply chain

- > To demonstrate to regulators that their auditors know what they are doing

A robust audit and self-inspection program, underpinned by skilled auditors, is vital in ensuring quality improvement is continuous and compliance risks are reduced. Our clients partner with us to:

- > Develop their entire external audit group
- > Develop new starters to their audit groups
- > Train their internal auditors through the program and then make sure they stay up-to-date by providing additional technical training as part of their continuous professional development



The Return on Your Investment

- > Shared best practices across the auditing group; consistency is key
- > Enhanced technical and interpersonal skills so vital in any audit
- > Consistent interpretation of standards
- > A real focus on continuous improvement and keeping things simple
- > A commitment to patient safety throughout based on good science and sound common sense!

Are your auditors performing value-adding audits consistently across your sites and suppliers?

Do you want real confidence in the quality of the audit program and the skills of your auditors?

Register now for **Effective Pharmaceutical Audits and Self-Inspections (An IRCA Certified Pharmaceutical QMS Auditor/Lead Auditor course, No A17638)**. If you are interested in bringing auditor certification in-house to train your internal and external audit teams please contact us.



by Mike Halliday,
Executive
Director, NSF
Health Sciences
Pharma Biotech
Consulting

Words of Wisdom

We now accept the fact that learning is a lifelong process of keeping abreast of change. And the most pressing task is to teach people how to learn.

Peter Drucker

For more information contact Mike Halliday, Executive Director at mikehalliday@nsf.org – For training enquires in the USA contact Austin Caudle at acaudle@nsf.org



by Martin Lush, President, NSF Health Sciences Pharma Biotech Consulting

Improving Human Reliability: Batch Record Simplification

A Case Study of What Is Possible!

For those of you who have attended our very popular *Human Error Prevention* course, you will know that many errors are caused by the very documents designed to prevent them. This applies to batch manufacturing records (BMRs) and SOPs in particular. These documents can often be:

- > Poorly designed
- > Difficult to follow with too many words and not enough pictures and schematics
- > Written by the wrong person using language the users simply can't understand
- > Often written for the auditor rather than the user
- > Too complicated, leading to brain overload

We worked with a major pharmaceutical company recently to help simplify its BMRs. This is what their staff have achieved using the tools and techniques we provided on a three-day simplification workshop.

Not a bad return on investment!

This is the process we used:

1. **Get the right people** in a room, off-site (no distractions) and with lots of flipcharts, food and drink! By the right people, I mean those who are knowledgeable, will speak their mind but are open to new ideas. Key representatives are needed from:
 - > Manufacturing, the primary user group. The presence of operators is vital
 - > QA (including the QP)
 - > Development
 - > Regulatory Affairs
2. **Select the BMR you want to simplify with care.** Don't go for the largest or most complicated. Cut your teeth on something a little easier in the first instance. You want to succeed. The more challenging BMRs can wait until later

Starting point: The BMR in 2011	Progress so far: The BMR in 2014
Review and approval time = 1.5 hours	Review and approval time reduced to 30 mins
237 pages	Simplification reduced BMR size to 72 pages
Right first time = 62%	Right first time = 96%
Number of signatures 110(!)	Signatures reduced to 23
BMR owned by QA	BMR owned by Manufacturing
Average number of errors/BMR = 28	Errors reduced to an average of 3
Order due date performance 76%	99% of batches released on time

3. **Get the group to agree on the core purpose of the BMR.** This is not as easy as it sounds, as everyone has a view. But for clarity, the BMR exists to:

- > Provide essential instruction for the users
- > Provide a reliable history of events: the who, what, when, where, how and what if (problems)
- > Provide enough information for QA releasing officers (QPs) to confirm the batch has been made to GMP and is safe, effective and of the right quality

4. **Get the individual groups working.** Ask each group to take a copy of the BMR and a fistful of highlighter pens (low-tech is always simpler, better).

- > The regulatory affairs team focuses on highlighting parts of the BMR that are referenced in licensed documents
- > Your development people are charged with highlighting process critical control points that directly impact on product quality
- > Your operators and manufacturing colleagues' job is to highlight essential instructions needed to do the job
- > Your QA folks focus on highlighting essential GMP requirements

5. **Managing the input: Starting the simplification process.**

- > Get an electronic copy of the BMR up on a screen for all to see
- > Go through the BMR line by line, page by page
- > Each group decides what must stay (the highlighted text) and what can be removed to the electronic waste bin
- > Take a break (trust me, you will need it) and revisit the waste bin. Apply simple risk assessment to see if what you have removed should stay removed, or not. Resist putting information back "just in case"

> At the end of this process you have taken the BMR back to basics. Now that you have removed unnecessary content, you can focus on...

6. **Redesign of the BMR.**

- > Print out the information
- > Grab some scissors and glue (this is the bit most adults really enjoy)
- > Redesign the BMR the old fashioned way, ie by cutting out the key steps and arranging them in a chronological flow chart

One health warning. This is not as simple as it sounds – it's actually very hard work. Follow this process and you will get differences of opinion, arguments and resistance to change driven by fear of the unknown and, on occasions, lack of trust. But simplification reduces ambiguity and error; and everyone will always agree to avoid complexity.



If you would like **more information on the above process**, please do get in touch with our simplification experts, Martin Lush (martinlush@nsf.org) or John Johnson (johnjohnson@nsf.org). We have hard-won experience in this field and a proven approach used across a range of cultures, pharma dosage forms and technologies.

If you're passionate about simplification, sign up to our **FREE webinar** on June 11th, *The art and science of simplification – how to win your war on complexity*, scan the code alongside.

...and don't miss NSF Health Sciences' Human Error Prevention group on LinkedIn, scan the code alongside.



Rapid Change Control

Is Your Change Control System Fit for Purpose?



by Martin Lush, President,
NSF Health Sciences
Pharma Biotech Consulting

Use this free “health check” to find out

Charles Darwin famously said:

“It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change.”

In the struggle for survival, the fittest win out at the expense of their rivals because they succeed in adapting themselves best to their environment.”

The same applies to pharmaceutical companies. Those that can adapt to the rapidly changing environment will succeed. Those that can't won't. Pete Gough's regulatory update in each Journal always provides valuable

insight to what is on the horizon, and there is always something! Combine these regulatory changes with those many of you routinely face and the challenge to your change control systems is considerable. Changes related to buildings, processes, equipment, procedures, systems, third parties, organization... they all have to be reviewed and assessed quickly.

In short, the speed and effectiveness of your change control system is crucial to your future success.

So, is your change control system fit for purpose? Is it fast and robust, and at the same time flexible and effective? Use the following “health check” to find out. Get together with a few users of the system and answer the following 10 questions with a simple *yes* or *no*.

If you have answered *yes* to all of the questions, congratulations, your system is fit for purpose. Darwin would be pleased. If you have a few *no*'s, please let us help you – register for our course on Rapid Change Control.

Don't worry...you don't have to completely re-engineer your system to improve it. We will provide you with tools and techniques (and a few shortcuts) that you can implement with ease. See you in Manchester in July!

- | | |
|---|--|
| 1. Is your change control system owned by all parties, not just QA? | Y <input type="checkbox"/> /N <input type="checkbox"/> |
| 2. Was your system designed by a multidisciplinary team including all user groups? | Y <input type="checkbox"/> /N <input type="checkbox"/> |
| 3. Can your change control system review and approve a change request in 30 minutes? | Y <input type="checkbox"/> /N <input type="checkbox"/> |
| 4. Does your change control system reject at least 30-40 percent of change requests? | Y <input type="checkbox"/> /N <input type="checkbox"/> |
| 5. Do you use a risk-based impact assessment form to assess change requests? | Y <input type="checkbox"/> /N <input type="checkbox"/> |
| 6. Is every change request supported by a business case (cost vs benefit)? | Y <input type="checkbox"/> /N <input type="checkbox"/> |
| 7. Is your change control procedure simple to understand? | Y <input type="checkbox"/> /N <input type="checkbox"/> |
| 8. Do you follow up every approved change to ensure it worked? | Y <input type="checkbox"/> /N <input type="checkbox"/> |
| 9. Have those responsible for implementing changes received training in change leadership? | Y <input type="checkbox"/> /N <input type="checkbox"/> |
| 10. Do you review and improve your change control procedure every year following consultation with all users? | Y <input type="checkbox"/> /N <input type="checkbox"/> |

Rapid Change Control Manchester, UK – July 2-3

What you will learn: The solutions you will leave with!

- How to review and approve changes within minutes not hours
- How to use your change control system to STOP unnecessary change so you can focus your time and resource on the 20 percent of changes that matter
- How to ensure that approved changes are implemented correctly and add value
- How to control change with your third parties so you can sleep easy at night
- How to audit change control systems properly
- The measures you can use to prove your system is working
- How to make people smile with enthusiasm when they talk about change control!



For more information on our training services, visit: www.nsf.org/training-education/training-pharma-biotech/

Regulatory Update



by Pete Gough,
Executive
Director, NSF
Health Sciences
Pharma Biotech
Consulting

EU News

Excipient Risk Assessment and GMP

On March 19, 2015 the final version of a Guideline on the formalized Risk Assessment to determine the appropriate GMP for Excipients was published in the Official Journal of the European Union. This final version is quite similar to the draft that was published in February 2013 and sets a deadline of March 21, 2016 for completing the required risk assessments.

API GDP Guideline

On March 19, 2015 the final version of a Guideline on GDP for APIs for Human Use was published in the Official Journal. This final version is again quite similar to the draft that was published in February 2013 but the requirements have been consolidated into fewer chapters.

Annex 1: Sterile Products

Annex 1 on the manufacture of sterile products is being revised again. A concept paper was published jointly by the European Medicines Agency (EMA) and the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) on February 5, 2015, with comments due by March 31, 2015.

This revision will be a complete re-write of the annex and will be led by Andrew Hopkins of the UK MHRA. The reasons for the update are to:

- > Include ICH Q9 and Q10 principles
- > Provide clarification and remove historical inaccuracies and areas of ambiguity
- > Capture new technologies such as the use of barrier systems (e.g. RABS and isolators) and the need to move away from open systems

> Provide guidance for WFI manufactured by technologies other than distillation

> Align with PIC/S and other international requirements where possible

The concept paper states that a draft revision is expected to be published in October 2015.

Annex 15: Validation

The final version of the revised Annex was published on March 30, 2015 and becomes effective from October 1, 2015.

Annex 16: QP Certification and Batch Release

The final version has been approved by the EMA Inspectors Working Party and is with the European Commission for final approval. It is expected to be published in June or July 2015.

Annex 20: Importation of Finished Product

Following the implementation of the Falsified Medicines Directive, there are now strict controls on the importation of APIs. It is now the intention of the EMA to produce equally comprehensive expectations regarding the importation of finished products and this is expected to eventually be published as Annex 20.

It is anticipated that a concept paper regarding this new Annex will be published in 2015 with a draft version of the Annex expected in 2016.

UK News

Data Integrity

The Medicines and Healthcare Products Regulatory Agency (MHRA) published Data Integrity Definitions and Guidance for Industry

in January 2015, and issued revision 1.1 of this guidance in March 2015. This guidance sets the expectation that companies should have a data governance system. This system should be designed and operated to provide an acceptable state of control based on the data integrity risk, and be fully documented with supporting rationale.

The guidance points out that data can take many forms, from simple paper records to printouts from instruments to data stored in complex computer systems. The risks to data integrity differ based on how it is generated and the extent and mechanism by which it can be manipulated.

The guidance states that systems should be designed to encourage compliance with the principles of data integrity. For example:

- > Access to clocks for recording timed events
- > Accessibility of batch records at locations where activities take place so that ad hoc data recording and later transcription to official records is not necessary
- > Control over blank paper templates for data recording
- > User access rights which prevent, or audit trail, data amendments
- > Automated data capture or printers attached to equipment such as balances
- > Proximity of printers to relevant activities
- > Access to sampling points (e.g. for water systems)
- > Access to raw data for staff performing data checking activities

The guidance requires that data must be ALCOA, i.e.:

A – Attributable to the person generating the data

L – Legible and permanent

C – Contemporaneous

O – Original (or 'true copy')

A – Accurate

The guidance provides definitions for many terms associated with the control of data and sets expectations for each where appropriate.

ICH News

ICH Structure and Membership

In January 2015, following a meeting in Lisbon in the autumn of 2014, the International Conference on Harmonisation (ICH) published a new governance structure under a new legal entity. This new legal entity will set up ICH as a non-profit association under Swiss law and should be functional by June 2015. This new structure consists of the following elements:

- > **ICH Assembly** The assembly will be comprised of the ICH Management Committee and ICH members. It will be the overarching body of the new association. Eventually ICH will be funded by membership fees that will be determined by the assembly.
- > **ICH Management Committee** This committee will be in charge of operational matters. Its primary role will be administration and financial matters.

The composition of the Management Committee will initially be the same as that of the former ICH Steering Committee (SC), as of January 1, 2015. The current SC members will become "permanent members" of the new management committee and the current observers will



Regulatory Update

become “permanent observers.”

After two years, new committee members may be elected by the assembly from among its members.

- > **ICH Members** ICH membership will be open to regulators and industry associations.

These structural changes within ICH are very significant and should eventually lead to ICH becoming a more global harmonization organization.

ICH Q3D – Elemental Impurities

The ICH Q3D Guideline for Elemental Impurities reached Step 4 of the ICH process in December 2014 and is being implemented (Step 5) in the three ICH regions. The Expert Working Group (EWG) will become an Implementation Working Group (IWG) to produce a Q&A document and examples to aid industry in implementation.

Initially the guide will apply to new finished products and new products containing existing drug substances. The guideline does not apply to ATMPs, herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives, dialysate solutions not intended for systemic circulation, and elements that are intentionally included in the drug product for therapeutic benefit.

The application of the new guideline will apply to existing products three years after the guideline is published.

Elemental impurities in medicinal products may come from a variety of sources including those added during chemical synthesis, those present in raw materials or those that result from contact with processing equipment. This guideline identifies elemental impurities that may have potential health/toxicology impact, establishes permitted daily exposure (PDE) of those impurities and addresses controls necessary to maintain the impurities below the recommended PDE.

The guideline requires that risk management (per ICH Q9) should be applied and documented. This can be boiled down to three simple steps:

- > **Identify** the sources of elemental impurities that are known or suspected, or have the potential to end up in the finished product
- > **Evaluate** the presence of a particular elemental impurity in the drug product by determining the observed or predicted level of the impurity and comparing with the established PDE
- > **Summarize and document** the risk assessment. Identify if **controls** built into the process are sufficient or identify additional controls to be considered to limit elemental impurities in the drug product

The guideline lists several controls that can be applied to reduce the level of elemental impurities.

Appendix 1 of the guide is a glossary.

Appendix 2 provides tables of the calculated PDE values for 24 identified elemental impurities.

Appendix 3 makes up the majority of the text and provides the individual safety assessments for each of the 24 elemental impurities.

Appendix 4 provides illustrative examples of the calculations to convert PDEs into permitted elemental impurity calculations.

US FDA News

In early February 2015 Margaret Hamburg announced that she was stepping down as the US FDA Commissioner in March. She is temporarily replaced by the FDA Chief Scientist, Dr. Stephen Ostroff, who was appointed Acting Commissioner.

Office of Pharmaceutical Quality (OPQ)

The Center for Drug Evaluation and Research (CDER) has created a new Office of Pharmaceutical Quality (OPQ), which became fully operational in January 2015.

The OPQ is a “super office” that will oversee manufacturing quality throughout a drug’s lifecycle. OPQ will have specialized staff for product review and for inspections, with specific units to handle active pharmaceutical ingredients, new drugs, biotech products and generics. The new OPQ has eight subordinate offices:

- > Office of Program and Regulatory Operations (OPRO)
 - The OPRO is accountable for the business process, QMS, etc. within OPQ
- > Office of Policy for Pharmaceutical Quality (OPPQ)
 - The OPPQ is responsible for developing and communicating product quality policies and standards
- > Office of Biotechnology Products (OBP)
- > Office of New Drug Products (ONDP)
- > Office of Lifecycle Drug Products (OLDP)
 - The OLDP has two main functions: post-marketing quality assessment of branded products and pre- and post-marketing assessment of generic products
- > Office of Testing and Research (OTR)
- > Office of Process and Facilities (OPF)
 - The OPF will ensure that quality is built into manufacturing processes and facilities over the product lifecycle
- > Office of Surveillance (OS)
 - The OS will oversee quality performance at facilities through pre-approval and routine inspections, with an eye to evaluating if an operation meets performance metrics that indicate a quality operation. It will develop a comprehensive risk ranking of all sites

SUPAC Manufacturing Equipment Addendum

In December 2014, the FDA released the final version of its guidance on scale-up and post-approval changes (SUPAC) that combines and supersedes the following previous SUPAC guidance documents:

- > SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms, Manufacturing Equipment Addendum
- > SUPAC-SS Nonsterile Semisolid Dosage Forms, Manufacturing Equipment Addendum

This new guidance removes the lists of manufacturing equipment that were in the previous guidance documents and clarifies the types of processes being referenced.

The FDA said that it will assess proposed changes based on the types of equipment changes being considered. The new SUPAC addendum should be used in combination with the other SUPAC guidance documents and is not mandatory. FDA states that alternate approaches will be acceptable providing that they are supported by a suitable risk-based assessment.

Draft cGMP for Combination Products

In January 2015, FDA issued draft Good Manufacturing Practice (GMP) guidance for combination products. This guidance describes and explains the final rule on current GMP (cGMP) requirements for combination products (as codified in 21 CFR part 4) that FDA issued on January 22, 2013.

The draft guidance gives combination product manufacturers two options for GMP compliance: satisfy all drug and device GMPs, or implement a streamlined quality system that focuses primarily on one but incorporates elements of the other.

The guidance details what GMPs are applicable to a product, general methods for how to implement them, key definitions and how to make post-market changes to a product’s quality system. The draft also shows how to develop a streamlined system using three detailed product scenarios: a pre-filled syringe, drug-coated mesh and a drug-eluting stent.

The draft guidance also provides expectations for the management of contract manufacturers.

Forthcoming Courses

What's planned for July – October 2015



Our EU Career Path Key

- Active Pharmaceutical Ingredients/Excipients
- Audit/Self-Inspection
- Biopharmaceuticals/Biotechnology
- Clinical Trials/Investigational Medicinal Products
- Good Manufacturing Practice
- Laboratory Management/Quality Control
- Pharmaceutical Law/Regulatory Affairs
- Pharmaceutical Manufacturing
- Qualified Person Training
- Quality Management Systems
- Risk Management
- Senior Management
- Statistics
- Sterile Products
- Supply Chain and Distribution



Rapid Change Control

Is your change control system fit-for-purpose? Find out, and leave with solutions you can implement with ease.

July 2-3

Renaissance Manchester City Centre Hotel, Manchester, UK



Human Error Prevention

Tools and techniques to reduce errors, protect your business and drive continuous improvement.

September 16-18

Amsterdam Marriott Hotel, Amsterdam, The Netherlands



A-Z of Sterile Products Manufacture

Air change rates to Z values... and everything in between.

October 5-8

Amsterdam Marriott Hotel, Amsterdam, The Netherlands



Pharmaceutical Law & Administration

Get a thorough understanding of the laws and legal processes in an increasingly changing world.

October 19-23

York Marriott Hotel, York, UK



The Role & Professional Duties of the Qualified Person

How the QP should conduct themselves in discharging their legal duties – includes simulation of a UK QP interview.

July 20-23

York Marriott Hotel, York, UK



Effective Pharmaceutical Audits and Self-Inspections

An IRCA certified Pharmaceutical QMS Auditor/Lead Auditor course.

September 21-25

York Marriott Hotel, York, UK



How to Audit – Sterile Products Manufacture

Where the risks lie, what questions to ask and how to assess whether processes are under control.

October 9

Amsterdam Marriott Hotel, Amsterdam, The Netherlands



Free QP Seminar for Prospective QPs & Sponsors

Interested in training to become a QP or want to know about sponsoring a QP? Come along and find out more.

October 20

York Marriott Hotel, York, UK



Mathematics & Statistics

The ability to trend and analyze data is an essential survival skill – learn how to do this simply and effectively.

September 14-17

Hilton York Hotel, York, UK



Risk-Based Decision Making for Quality Professionals and QPs

Detecting, assessing and mitigating risks is crucial. Find out how to do it quickly, accurately and with proven return on investment.

September 29-30

Manchester Marriott Victoria & Albert Hotel, Manchester, UK



Pharmaceutical Legislation Update

Keep up-to-date with the latest regulatory requirements.

October 6

Manchester Marriott Victoria & Albert Hotel, Manchester, UK



Good Autoclave Practice

Practical guidance for sterilizer compliance.

October 21-23

Hilton Hyde Park Hotel, London, UK



A full, up-to-date course listing is available online

How to Reduce Repeat Deviations: 5 Key Steps

How good is your Deviation and CAPA system, or are you at risk?

September 14-15

Amsterdam Marriott Hotel, Amsterdam, The Netherlands

Early Bird or Multiple Delegate discounts apply to some of our courses. Please visit our website, www.nsf.org, for full details.

For more information www.nsf.org/info/pharma-training

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

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Words of Wisdom

There is no end to education. It is not that you read a book, pass an exam and finish with education. The whole of life, from the moment you are born to the moment you die, is a process of learning.

Jiddu Krishnamurti



Course Calendar May – December 2015

May

- 11 **Effective Pharmaceutical Audits and Self-Inspections**
(An IRCA Certified Pharmaceutical QMS Auditor/Lead Auditor Course) ~ 5 days
- 18 **Pharmaceutical Microbiology** ~ 5 days
- 19 **Free Seminar for Prospective QPs & Sponsors** ~ 1 day

June

- 1 **How to Audit – Data Integrity** ~ 1 day
- 2 **How to Audit – QC Chemical Laboratories** ~ 2 days
- 4 **QP Alumni** ~ 2 days
- 15 **Active Pharmaceutical Ingredients** ~ 4 days
- 16 **Modern Approaches to Process Validation** ~ 3 days
- 19 **How to Audit – Chemical API** ~ 1 day
- 22 **Risk-Based Decision Making in Sterile Products Manufacture** ~ 4 days

July

- 2 **Rapid Change Control** ~ 2 days
- 20 **The Role & Professional Duties of the Qualified Person** ~ 4 days

August

September

- 14 **How to Reduce Repeat Deviations: 5 Key Steps** ~ 2 days
Mathematics & Statistics ~ 4 days
- 16 **Human Error Prevention** ~ 3 days

- 21 **Effective Pharmaceutical Audits and Self-Inspections**
(An IRCA Certified Pharmaceutical QMS Auditor/Lead Auditor Course) ~ 5 days

- 29 **Risk-Based Decision Making for Quality Professionals and QPs** ~ 2 days

October

- 5 **A-Z of Sterile Products Manufacture** ~ 4 days
- 6 **Pharmaceutical Legislation Update** ~ 1 day
- 9 **How to Audit – Sterile Products Manufacture** ~ 1 day
- 19 **Pharmaceutical Law & Administration** ~ 5 days
- 20 **Free Seminar for Prospective QPs & Sponsors** ~ 1 day
- 21 **Good Autoclave Practice** ~ 3 days

November

- 2 **Effective Pharmaceutical Audits and Self-Inspections**
(An IRCA Certified Pharmaceutical QMS Auditor/Lead Auditor Course) ~ 5 days
- 9 **GMP for Clinical Trials Manufacture and Supply** ~ 4 days
Pharmaceutical Quality Systems: Best Industry Practice ~ 3 days
- 12 **Managing Costs of Poor Quality** ~ 2 days
- 16 **Analysis & Testing** ~ 5 days
- 23 **Pharmaceutical GMP** ~ 3.5 days

December

- 1 **Good Distribution Practice** ~ 2 days

For more information www.nsf.org/info/pharma-training



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