Journal

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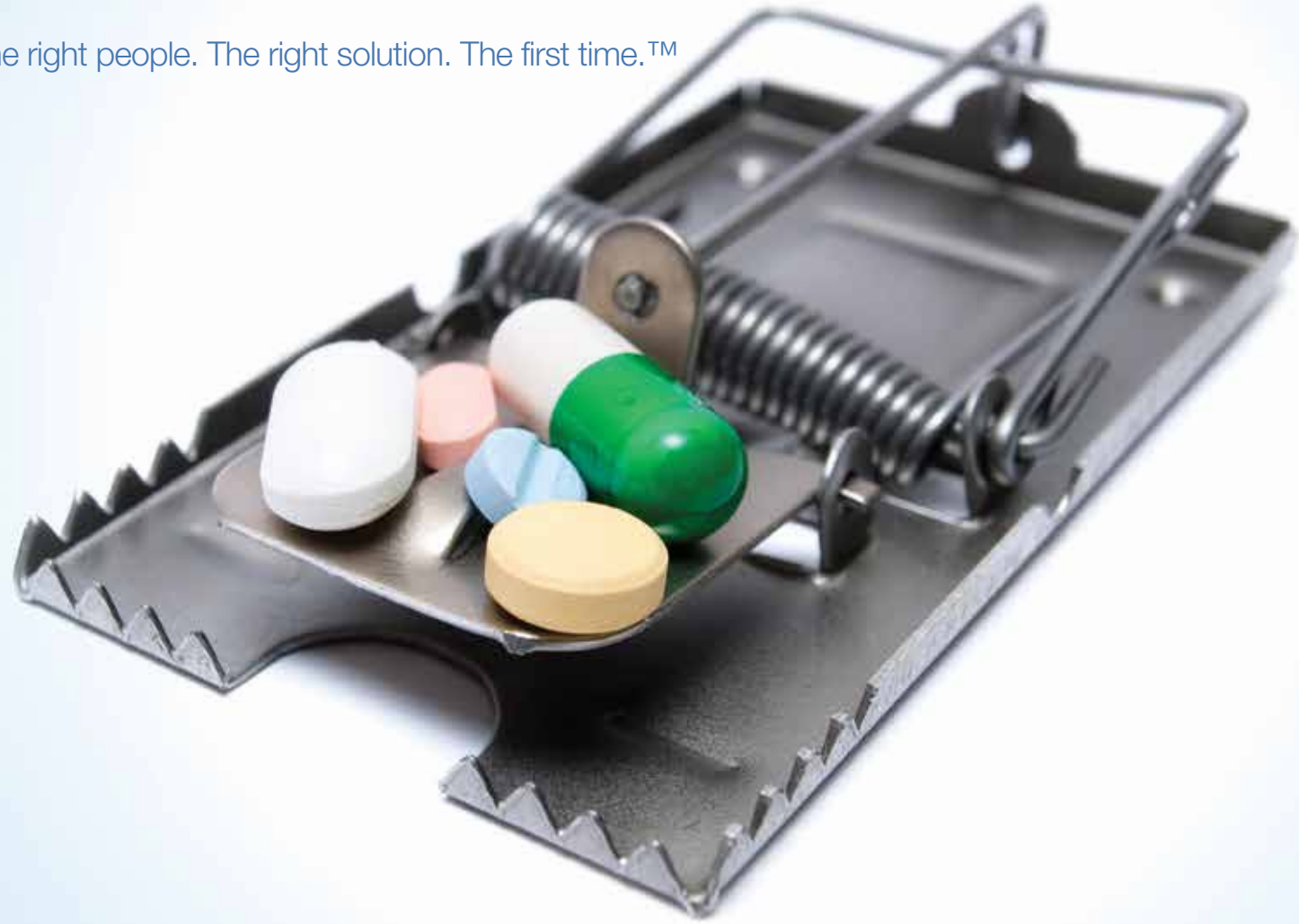
The right people. The right solution. The first time.™



What is the **Biggest Risk** Facing Your Company?

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NSF Health Sciences
Pharma
Biotech

Formerly NSF-DBA

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welcome

Life-Threatening Drug Shortages: A Solution!

Just before I left to present at the ISPE Europe annual conference in Frankfurt (and an excellent event it was), I was tackled by my local pharmacist. I was attempting to collect a prescription for my son,… but it was not available. I wasn't the only disappointed customer that day. In fact, he said the shortage of medicines was the worst he had ever seen in 20 years! And, of course, he had every right to ask the obvious question – "Why can't the industry maintain an adequate supply of pharma products?"

One day later I participated in an ISPE session dedicated to drug shortages. The numbers and statistics are worrying. Deming would be turning in his grave listening to this debate. His advice would be simple… **if you want to stop drug shortages, just do the basics well.** Here are four tenets that reduce the risk of shortages:

- Have **reliable processes**
- Operated by **well educated, knowledgeable people**
- Using **simple, robust systems** designed by users
- In a culture of **continuous improvement** where problems and mistakes are seen as learning opportunities.

At the end of the excellent presentations, I posed the panel this question: "What is stopping the pharmaceutical industry doing what every other manufacturing industry has done for decades…?" namely, delivery of the basics of 'right first time, every time', using the four tenets for risk reduction shown above.

At NSF Health Sciences our objective is to help you do the basics to PhD level and to help you to deliver high quality medicines on time in full.

Our education courses described on pages 22-27 are designed to help you excel at doing the basics and change behaviors in the workplace. The articles in this edition of the Journal are designed to do the same. Simple, readable, provocative and informative.

Happy reading!

Martin Lush

Martin Lush
President,
NSF Health Sciences
Pharma Biotech

Tech Talk

Do Particulates Matter…?

9 recalls in USA already this year suggest they do!

The visual appearance of sterile drug products is obviously a key quality attribute for any formulated product, yet the pharma industry still struggles to define, control and set in place effective monitors. Freedom from particulates has been a compendial requirement for three decades so why is it that there are typically two to five US recalls per month that cite a lack of assurance of visual quality causing a perception of significant patient risk? Why is the industry struggling to prevent foreign body contamination in parenteral formulations and why is the market clearly still experiencing drug shortages due to recalls of this nature?

When faced with either single or multiple customer complaints (always linked to field alerts in the USA), or when identifying concerns while batches are still in the factory, what questions are you faced with?

- The most crucial concern will be associated with the effect on patient safety: Does the event create a risk to the patients?
- Does the event represent a case of adulteration or breach of registered specifications?
- Does the event appear to be a significant quality defect?
- Does the event undermine corporate branding or diminish customer confidence?

In the case of patient safety, despite some historical references to animal testing proving negligible human risk, foreign body contamination is still noted by regulators as an unacceptable quality defect, largely because registered specifications, compendia and end users demand this to be the case. After all, who would readily inject or infuse a product into an injured or ill person knowing that it contained visible foreign body contamination?

In all cases, firms utilize their medical practitioners and QA teams to help write a medical risk assessment that will take into account:

- Biological activity and toxicity of the particle and any relevant leachables
- Route of administration and aspects of absorption, distribution, metabolism and excretion of the particle
- Size, shape and origin of the particle
- Potential of the particle to harbor microorganisms
- For biotech products, any risk of immunogenicity or aggregation

A key risk occurs when particles at the edge of visual detection (~20 microns) enter the injection site because they can then be distributed readily to pulmonary capillaries. Larger particles are easier to detect on administration, tend to remain close to the injection site and, though painful, are unlikely to be fatal. Other key effects can include phlebitis, inflammation, granuloma formation, occlusions, fibrosis, thrombi, microemboli

by John Johnson, Executive Director, NSF Health Sciences Pharma Biotech

Expert at GMP remediation but passionate about education, continuous improvement tools and mentoring of senior managers – John brings insight and sustainable pragmatic solutions based on 20 years as a QP and site/corporate leadership since 1998.

and immunogenic/antigenic reactions. It is also important to remember a tragic event in the USA in 1994, when two patients died from pulmonary emboli from calcium precipitates in an IV total nutrient mixture. In the UK in 1988, polypropylene shards from a syringe caused a small bowel infarction that led to the patient's death. Granulomas found in Puntis' post mortem study in 1992 of 41 TPN-fed patients were linked directly to cotton fibers and glass fragments. These cases are individually very disturbing, yet represent only a small fraction of deaths tied to particulates.

Obviously, it is vital that your quality system can:

- Prevent particles appearing in formulations
- Detect the key sources of risk throughout the process
- Remove them by visual or automated inspection

So where are these defects coming from?

According to Dempsey and Webber's article Hazards of Particle Injection (Pharmaceutical Journal, July 1983), the most common source of particles is from the rubber stopper with coring (during needle penetration), closely followed by glass particles, fibers, hair and crystal formation.

In terms of prevention and detection/removal of particle contamination, NSF Health Sciences recommends a five point plan:

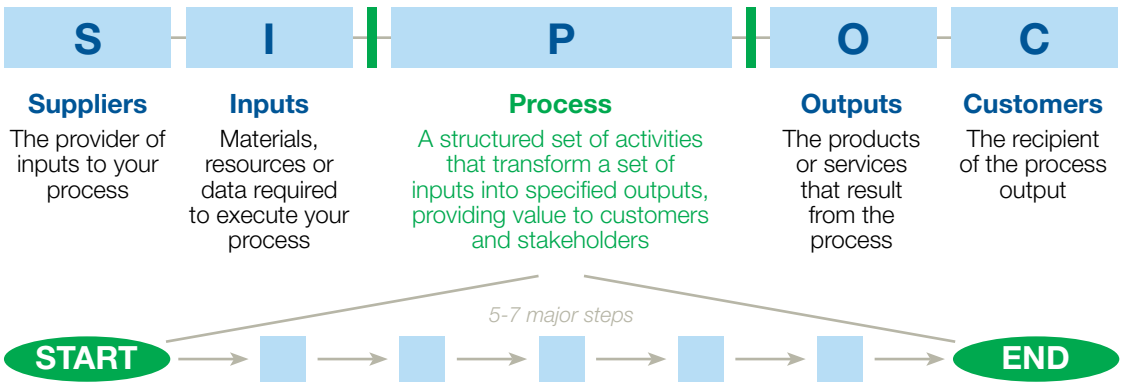
- SIPOC style risk assessments conducted throughout the production process by the area owners, but facilitated by a VI expert
- Relentless observation of best practices during sampling, gowning, processing and inspection; ensuring your team is based on the shop floor ensuring short interval control and monitoring of adverse conditions
- Extension of your quality system to your suppliers; cutting the risk of particulates at the source
- Robust processes for selection, education, supervision and periodic monitoring of any staff involved in manual inspection (production and QC inspection)
- Employment of validated automated visual inspection equipment; subject to detailed short interval checks and calibrations

In conclusion:

- The overall patient safety risk for macroscopic, biologically inert particles is relatively low though this depends on the health of the patient and the route of administration
- The presence of foreign bodies should be seen as an indicator of process capability and can signal a process out of control
- Zero defects is an aspirational target and can be used to drive continuous improvement, but is not a workable acceptable criterion
- Large molecule bioproducts need special considerations as do large volume parenteral formulations

If you recognize any of these concerns in your operation, please contact NSF as we have significant technical expertise in helping to diagnose the issues, assessing the impact and mitigating the risks. Our research shows that sterile manufacturers still struggle to contain this issue and we are active in supporting their efforts to protect their customers and in turn their future business.

Figure 1. SIPOC – understanding processes



NSF Health Sciences Pharma Biotech

Our services in French, German and Italian have become a huge success!

Over the last 28 years, we have built a worldwide reputation for providing high quality pharmaceutical consulting and training – in English!

In 2012, we decided to expand on this, so we carefully sought out and hired a team of experienced industry professionals to provide the same quality of services, but in French, German and Italian. This has proved more successful than we could possibly have imagined!

Last year we delivered the following services in French, German and Italian…

- 217 days of training on a wide variety of subjects, including:
  - General GMP
  - An update on new and upcoming international regulations
  - Modern approaches to quality management
  - Human error prevention
  - GMP for sterile products manufacture
  - 80 days of auditing and consulting to prepare companies for regulatory agency inspections, including FDA pre-approval inspections

All these services were enthusiastically received by clients and we continue to work with them to provide additional support and expert assistance.

We now have a formidable team of six French speaking consultants, seven German speaking consultants and 10 Italian speaking consultants and they are all highly experienced in European and US GMP requirements and are skilled and enthusiastic trainers. We specialize in listening to your needs and offering customized solutions to help you assure product quality and regulatory compliance.

If you are looking for the very best pharmaceutical consulting, auditing or training in French, German or Italian, why not try us? We know you won't be disappointed!

For more details and a competitive quote, contact **Stephen Engels** at **sengels@nsf.org**

Look out for us at the AFI Symposium, 11-13 June, in Rimini

by Stephen Engels, Principal Associate, NSF Health Sciences Pharma Biotech Europe

30 years' experience in pharmaceutical manufacturing, QA, regulatory compliance and quality systems. Now leading our team of Italian, German and French speaking Associates in mainland Europe.

Words of Wisdom

"This journey is not over. Our education initiatives have so much momentum, and we're committed to sharing even more."

Ann Bancroft

Is Your Biggest Business Risk COMPLACENCY?

Words of Wisdom

"Success breeds complacency. Complacency breeds failure. Only the paranoid survive."

Andy Grove

The Complacency Test:

Any of the following sound familiar?

- ☐ Recently passed a successful regulatory audit…and breathed a huge sigh of relief?
- ☐ Does your senior management think a successful regulatory audit is the "end game"?
- ☐ Are you drowning in key performance indicators that tell your leadership what they want to hear rather than the painful truth?
- ☐ Repeat deviations still an issue?
- ☐ Struggling to complete deviation investigations within 48 hours?
- ☐ Do you reward people for driving down deviation incidents?
- ☐ Has firefighting become such a habit you don't even notice it any longer?
- ☐ Ever read another company's 483s and thought they sounded familiar?
- ☐ Does your leadership spend more time in meetings than on the shop floor?
- ☐ Is your company severely risk averse?
- ☐ Suffering from initiative overload, when nothing gets done properly?
- ☐ Frustrated by poor communication and the time wasted on internal politics?
- ☐ Do you see training as a cost, not an investment?
- ☐ Does your company take the attitude "If it isn't broke, don't fix it"?
- ☐ Do you think what worked yesterday will be good enough today?
- ☐ Does your quality management look the same as it did five years ago?

Too many yes answers should ring a few alarm bells. You may be at risk from the silent killer at many organizations…COMPLACENCY. Just ask BlackBerry (everyone used to have one), Nokia (previous market leaders) and Kodak. The list is endless and includes a few big names in pharma too.

Companies who took their eye of the ball and saw their market share, legacy and reputation destroyed by consent degrees, warning letters and importation alert bans. In short, they all became complacent.

Jim Collins' books 'Good to Great' and 'Great by Choice' should be required reading for everyone. These books are a highly forensic (and readable) analyses of how companies achieve sustainable growth in difficult times. Here are two tremendous one-liners from Jim Collins:

- "Good is the enemy of great."
- "Companies that succeed work very hard at becoming productively paranoid."

How to Become "Productively Paranoid"

At NSF Health Sciences, we work in partnership with our clients to help them become productively paranoid:

- Our global client base, strong industry networks and links with regulatory agencies and governing bodies allow us to keep our finger on the regulatory heartbeat and industry pulse for pharma and medical devices
- Our regulatory experts can tell you what's coming and how to prepare
- Most of our team members have over 30 years' hands-on industry experience. We know what works and what doesn't, and we have walked in your shoes
- We have a reputation for challenging the status quo based on sound science, pragmatism and a genuine desire to help clients move from good to great. In an ever changing world we don't think "good" is good enough any longer
- We focus on changing people, not just improving systems. Without changing the way people think, you can't change anything

Hints for Productive Paranoia: What you must do

Here's what you MUST DO to overcome complacency.

Measure what matters most: Less is more

We believe the more you measure, the less you know. Make your KPIs focused and meaningful, more leading than lagging, and make sure they drive the right behavior.

Provide visible supervision and leadership: The best form of performance management is vigilant supervision

We believe leadership at every level should spend more time where they add greatest value – on the shop floor "walking the talk." Only then will they get a sense of the challenges their teams face on a daily basis. How else can you see where improvement is needed?

Break the firefighting habit: Develop an unrelenting passion for continuous improvement

We believe deviations provide a fantastic opportunity for improvement and that people should be rewarded for raising them. We think incidents should be treated as a priority, triaged (risk ranked) and investigated in hours, not days, by educated (certified) problem solvers.

Give power to the people: Engage your entire workforce…they are just waiting to be switched on

We believe most companies only utilize 10% of the intellectual capability of their workforce. The skills and competencies of operators and junior staff usually remain untapped. When we help our clients move from "good to great," we help to improve their core competencies so they are equipped to complete root cause investigations and internal self-inspections and to drive continuous improvement.

Conduct internal audits and self-inspections: Your catalyst for productive paranoia

We believe a risk-based internal audit and self-inspection program is key to identifying your strengths and weaknesses needed to drive continuous improvement and manage risk. To have confidence in your audits, you must have confidence in your auditors by providing them with the skills and knowledge to do a tough job well. Don't let the first time you know of a problem be when your EMA or FDA inspector identifies it for you. The key is self-identification. Anything less and the control of the business moves from you to someone else. Don't let complacency allow control to slip away.

continued overleaf

by Martin Lush, President, NSF Health Sciences Pharma Biotech

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

…continued

Is Your Biggest Business Risk COMPLACENCY?

Words of Wisdom

"The best we can do is size up the chances, calculate the risks involved, estimate our ability to deal with them, and then make our plans with confidence."

Henry Ford

Benchmark: Learn from the best

We believe as soon as you think that "good is good enough," you are in trouble. You have to constantly challenge, question and improve… but not reinvent the wheel. We have worked very closely with best-in-class companies in pharma, automobiles and the retail sector. If you want to learn about what works and simple solutions to complex problems, our Quality System Benchmarking workshop will help.

Educate for the future: Don't train for the past

We are amazed how many companies stick with compliance-based training that tells people what to do without explaining why. At NSF Health Sciences, we believe in helping to educate our clients for the future, not training them for the past. Our clients tell us that our methods have changed behaviors in the work place, not just checked the compliance training box. If you want an educated workforce capable of doing more with less, our 'From Training to Education' workshop will transform your approach.

Focus on doing the basics to PhD level: Stop doing the rest

We believe your success is determined by what you stop doing. We help our clients focus on what really matters by helping them develop excellence in their products and processes, risk-based decision making, problem solving, error reduction and auditing.

In Summary: To Survive You Must Excel at Becoming Productively Paranoid!

- Complacency is silent. History tells us it can be deadly
- As soon as you stop challenging, questioning and improving, your days are numbered. Whether you call it arrogance or insularity, both can be equally damaging. Just ask BlackBerry, Nokia and Kodak
- Create a culture of productive paranoia…and fast
- NSF Health Sciences is obsessed by helping you prepare for the future, not the past
- If you want to protect your business from the danger of complacency, please give us a call on **+1 857-277-0060** in the US and **+44 (0)1751 432999** in the UK. We can help:
  - Our independently certified **Pharmaceutical Auditor education program** provides your auditors with the skills they need
  - **Benchmarking**. If you want to know how you compare with the best in class, we can help
  - **We help you do the basics to PhD level**. Our education programs on GMP, manufacturing processes, deviation and CAPA, and risk-based decision making are all designed to improve workplace behaviors and engage the 90% of your people waiting to be switched on
  - Our **free regulatory updates do just that.** Keeping you informed of what is coming as well as offer practical, no nonsense guidance on interpretation and implementation
  - Our hugely popular '**From Training to Education'** workshop is helping companies move from training that changes little to education that transforms workplace behaviors

For more information contact Martin Lush, President of NSF Health Sciences, at **martinlush@nsf.org** or John Johnson, NSF Health Sciences Executive Director, at **johnjohnson@nsf.org**. Martin can also provide you with a pharmaceutical overview of Collins' *Good to Great* and *Great by Choice* free of charge.

What's the Difference Between 10/20/70 and 70/20/10?

by Martin Lush, President, NSF Health Sciences Pharma Biotech

Answer: The Effectiveness of Your Education Program

Some startling facts about traditional training:

- When training activities are confined to a classroom, they usually fail to change behavior in the workplace. This wastes time and money
- When PowerPoint training is conducted in a classroom, it will never succeed in changing or improving anything
- Most people forget upwards of 90% of what is covered in a PowerPoint-based session within 24 hours. Their old habits and behaviors remain unchanged
- The more the presenter or trainer talks, the less the trainee learns
- Unless new behaviors and learning are reinforced immediately after the session they will be forgotten. It takes time and practice for new patterns of behavior to become established and for the theory to translate into action
- To change behaviors use the 10/20/70 rule:
  - 10% factual content – the basics
  - 20% practical exercises and immediate practice using case studies
  - 70% practical application, reinforcement and coaching in the workplace

However, most pharma training consists of:

- 70% factual content (PowerPoints)
- 20% practical exercises and immediate practice using case studies
- 10% practical application, reinforcement and coaching in the workplace… if any

If you understand the difference between 10/20/70 and 70/20/10, congratulations; you understand the difference between education and training. Education (the 10/20/70) succeeds in improving workplace behaviors whereas training rarely does. We're passionate about providing a return on your education investment. **We try and apply the 10/20/70 rule wherever possible with our courses**. They are interactive, 'learner centric' and FUN!

Is Your Company 10/20/70 or 70/20/10?

In our experience there are two types of pharmaceutical companies: those who see education as a profit generator (with a 10/20/70 focus) and those who are stuck in the GMP compliance "training" rut where 70% of the time is spent with the trainer talking with virtually no time coaching or consolidating new procedure and practices.

The difference that will make the difference…

10/20/70 Companies: Characteristics

- Focus on education, not training
- See education as key to their future prosperity
- Educate for the future, not train for the past
- Consider education as a profit generator
- Focus on improving behaviors in the workplace
- Have education programs that cover the why, not just the how

Words of Wisdom

Sustaining an audience is hard. It demands a consistency of thought, of purpose, and of action over a long period of time.

Bruce Springsteen

- Have skilled educators (learning coaches), not trainers

70/20/10 Companies: Characteristics

- Focus on training that doesn't improve behavior
- Train for the sake of compliance, not prosperity
- Train for the past, ignoring the skills and knowledge needed to remain competitive in the future
- See training as a compliance-driven cost center; something to be done as quickly as possible
- Focus on classroom-based information overload, ignoring coaching and reinforcement of new skills in the workplace
- Have programs that just cover the 'how' and ignore the 'why'. People know what buttons to press, but not why. The importance of the product, the impact they have and the patient are often ignored
- Have sessions presented by trainers who talk at the participants, with little two-way discussion, thus guaranteeing minimal real learning

A 10/20/70 Case Study: Education in Deviation and CAPA

One of our clients, concerned by unacceptably high levels of repeat deviations, conducted its own training course on root cause investigations. The result of this 70/20/10 training approach was that nothing improved. Repeat incidents continued to grow. The company called NSF Health Sciences to take a more educated approach. Twelve months after completing our education in deviation and CAPA, **repeat incidents have fallen by 35%...** not a bad return on investment. The behaviors of those investigating deviations have dramatically improved, as have teamwork, respect for each other and the delivery of scientifically justifiable rationales for key decisions. **This is how we did it.**

The 10%

We covered the factual content very quickly using high levels of interaction and engagement.

The 20%

We then moved onto the practical application of this knowledge using very carefully designed case studies and practical problem solving exercises designed with the client in advance. Participants were actually involved in solving their own deviations! When they struggled, we introduced a new problem solving method. After each exercise, we then presented the model answer and got them to share their lessons learned: what they did well and what they will do differently next time. In all, they practiced and refined these tools and techniques on each of the remaining 12 case studies until they had become automatic. Our course tutors provided constructive feedback and coaching throughout. The case studies were made as real life as possible. They were given too much data (leading to confusion and overload) and too little data in equal measure. We also provided them with very simple investigation templates to use and a very simple, structured problem solving processes. The group also agreed to a set of '5 Golden Rules' for deviation investigations.

The 70% That Matters!

By using the templates and allowing an NSF tutor to mentor the report owner, decision making process flows, the Golden Rules habits and behaviors practiced in the classroom were reinforced in the workplace. In addition, deviation investigations and reports completed by participants were reviewed and feedback provided so that a high standard was set, monitored and reinforced so that it became second nature. As Rommel said in 1942, "sweat saves blood" and our process of practicing in the workplace, with live cases and living the issue with the client, invariably sets a marked change in attitude and aptitude.

Action Points

- The 10/20/70 education approach works. The alternative doesn't
- If you would like to transform your traditional training approach to one that educates and improves workplace behaviors, please give us a call at **+1 857-277-0060** in the US and **+44 (0)1751 432999** in Europe. Our 'From Training to Education' workshop will help you move from 70/20/10 to 10/20/70!
- **If you want to drive down your level of repeat deviations, we have a well-tested and proven 10/20/70 model that works**

Our 'In-House' Education Programs Are Now More Accessible

Our courses delivered at the client's location have always been very popular. Content is customized to meet your exact needs and requirements and we come to you! This saves you time and money and minimizes inconvenience to busy work schedules. We have now introduced a new pricing structure that will allow you to educate more people for less. If you would like more information, please contact Anne Davies, **amd@nsf.org**.

Our Passion – Guaranteeing a Return on Your Investment

In addition to our residential education program, where you come to us, we also provide customized in-house education where we come to you:

- When you call us, we get back to you within 24 hours
- You then talk to one of our team members so that we can fully understand your needs and requirements. This is FREE of charge
- With the information you provide, we customize the course using the 10/20/70 formulae. This is FREE of charge
- We then provide you with a customized proposal and a fixed price to keep things simple
- We make sure the course focuses on your processes, systems and problems. You come with problems and leave with solutions. Your questions get answered
- Our course tutors each have over 30 years' experience. They know more than any text book!
- After each session we offer a FREE post-course clinic so we answer any remaining questions
- We stay with you after the course. You have access to our subject experts for ongoing support and advice FREE of charge
- We come to you so you save on travel, hotel costs and time away from the office and your families

Next time you select a training provider, ask them the 10/20/70 question!

Expert Corner

How many plates do you have spinning?

I had a great question last month and felt that the answer warranted some space in the Journal as it touches on a number of elements in the pharmaceutical quality system and centers on one the most critical skills in the industry; namely, how to get the best from the team you work within.

The question was:

"What are the most effective ways of sustaining momentum across multiple projects or throughout a period of multiple activities? Is there a particular mindset needed for managing multiple simultaneous issues as opposed to be focused on a single activity?"

The modern pharma manager can often feel like a circus juggler, spinning a dozen plates on tiny sticks. If you look closely, the juggler uses some clever techniques that make the whole exercise look easy.

If you watched the same show every night for a week, the first thing that you would notice is that the juggler has a **process**. He has a start-up routine to get the plate spinning, and he does that routine without variations to ensure that the operation begins effectively. He watches the plate spin for a few seconds and using intense concentration (and with a few minor adjustments), gets it up to speed quickly. He then knows how long it will spin and will be back to check it at short intervals (using what we might call **in process effectiveness checks**). The juggler is also known for his off-stage drills where he practices and validates his technique, so that it becomes second nature.

So to run multiple projects, first of all, requires a structured process that has a detailed plan. The plan must be visible and structured. By doing this, the project manager can see at a glance if a project is going awry and needs intervention. The plan should be front-end loaded so that the job is well defined and kicked off meticulously, allowing for less oversight as further projects (or plates) start spinning. But how to keep the momentum going?

Recognize how tough the situation is for your team, walk in their shoes and help them be adaptable and resourceful

People skills are critical to the process. The way staff are mentored, engaged and trained will determine the success of the organization, particularly when the going gets tough. People need to have the "know-why" as much as the know-how so that they can make on-the-spot decisions when deviations or unplanned situations arise. And of course the effective manager has to be able to delegate a level of control to staff, who are shown the level of authority and responsibility that they can exercise in any given situation. Investing in people, and taking the time to show, discuss and demonstrate the skills that are needed, can often be disastrously overlooked.

But when the plates start wobbling, how can momentum be re-applied? That's when **recognition, encouragement and short interval support** can really make a difference. Recognize how tough the situation is for your team, walk in their shoes and help them be adaptable and resourceful – and by return they will respond with renewed energy.

Ultimately, when projects exceed the resources available, another key process is needed – **quality risk management.** Throughout a program of work, using QRM techniques to assess risk and assign priority is highly recommended. Using risk ranking, HACCP or FMEA techniques to document what needs to be kept spinning, what can be left wobbling and what has little consequence if left out of scope will allow the busy team to focus on what is truly important. ICHQ10 and a range of QRM techniques are fantastic tools for managing multiple priorities and a thorough grounding in these is vital for any project team.

My second question is a relatively straightforward one.

John Johnson (NSF Health Sciences Executive Director) responds to questions from the **Ask John** series and shines a light on quality risk management and preparing for regulatory inspections of pharma biotech facilities. Keep your questions coming in and John will respond directly to you and, for selected topics, will reply here in the Journal.

Focusing my team at our next FDA Team Biologics inspection

"I want to get my team focused so what are the top three items that will be inspected during our forthcoming pharma biotech pre-approval inspection?"

Without a doubt, the inspectors will want to review in detail:

1. Process control and effective change management systems; ensuring current and future production is bioequivalent to that performed during manufacture of the clinical trial batches
2. For each variation experienced during manufacturing and testing of the biotech product, the detail concerning identification methods, multi-faceted impact assessment, root cause analysis, CAPA definition, CAPA completion and the effectiveness checks performed
3. The parts of the quality management system that minimize the risk of misbranding, adulteration and non-compliance to the regulatory submission

So, keep the questions coming in and, if they don't appear in the Journal, don't worry as I will respond to you directly.

Words of Wisdom

"Success is not final, failure is not fatal: it is the courage to continue that counts."

Winston Churchill

Email your questions, remarks or words of wisdom for our Expert Corner to **AskJohn@nsf.org**

The Journal Issue 29, Summer 2014

Regulatory Update

by Pete Gough, NSF Health Sciences Pharma Biotech

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

EU Pharma News

An update to implementing the Falsified Medicines Directive (FMD) – Have you set this in place yet?

The European legislation designed to reduce the threat posed by counterfeit medicines and starting materials, the FMD Directive 2011/62/EU, started to be implemented from 2 January 2013 onwards. Whilst we are still awaiting the final versions of the implementing guidance on excipient risk assessments and API GMP, which are expected to be finalized before the end of 2014, the expectations for starting materials are now fairly clear. The single largest remaining uncertainty is around the requirements for "safety features".

In February 2014, it was reported that the European Commission had completed its impact assessment regarding the safety features required by Directive 2011/62/EU and was proceeding to draft a delegated regulation to propose that:

1. The composition, format and carrier of the unique identifier will be fully harmonized across the EU. The unique identifier will be placed in a 2D barcode and contain the manufacturer code, a serialization number, a national reimbursement number (if present), the batch number and the expiration date.
2. Medicine authenticity will be guaranteed by an end-to-end verification system supplemented by risk-based verifications by wholesale distributors. Medicines will be systematically verified before being dispensed to patients. Medicines at higher risk of falsification (returns or medicines not being distributed directly by manufacturers) will be additionally checked at the wholesaler level.
3. The repository containing the unique identifiers will be set up and managed by stakeholders; i.e. the European Stakeholder Model (ESM). National competent authorities will be able to access and supervise the database.

This delegated regulation is expected to be adopted by Commission in late 2014 at the earliest. Publication in the Official Journal of the European Union will then follow in 2015 after successful scrutiny by the European Parliament, European Council and World Trade Organization. This means that the provisions of the delegated regulation would not have to be implemented before 2018.

Clinical Trials Regulation

On April 2, 2014, the text of a new clinical trials (CT) regulation, which will repeal Directive 2001/20/EC, was approved by the European Parliament. The regulation is expected to be published in the Official Journal of the European Union shortly. The fact that the new legislation will take the legal form of a regulation will ensure that the rules for conducting clinical trials are identical throughout the EU. This is vital to ensure that in authorizing and supervising the conduct of a clinical trial, Member States base themselves on identical rules.

The need to make this change is being driven by the fact that the CT Directive 2011/20/EC has failed to ensure harmonization across EU Member States and has given rise to an enormous bureaucracy associated with running clinical trials in Europe. This, in turn, has led to a significant decline in the number of clinical trials conducted in the EU.

The main changes in the new CT regulation include:

- Different categories of clinical trials with the introduction of "low-intervention" clinical trials
- Applications for a clinical trial authorization (CTA) to be made through a single European Medicines Agency (EMA) portal
  - The sponsor to propose one of the Member States concerned to be the reporting Member State
  - Member States to agree who will be the reporting state if there are several concerned states willing to act as the reporting Member State
  - Timeframes to be specified for the assessment of the application
- The content of the CTA dossier to be harmonized in order to ensure that all Member States have the same information available and to simplify the application process
- Clinical trial data submitted in support of a clinical trial application to be based only on clinical trials recorded in a publicly accessible and free-of-charge database
- Fostering of clinical research for the development of orphan medicinal products
- Electronic Web-based database reporting of adverse events and serious adverse events, and for annual reporting

EMA Regulation on Process Validation

CHMP Guidance

On February 27, 2014, the EMA published the final version of the revision of the CHMP Guideline on Process Validation that replaces the existing CHMP guidance on this topic (CPM/QWP/848/96 and EMEA/CVMP/598/99). The revised version becomes effective on August 27, 2014.

Unlike the 2011 FDA guidance on process validation, this revised guidance states that it does NOT introduce new requirements for medicinal products already authorized and on the market.

The final CHMP guidance states that the product lifecycle consists of three stages and that this guidance covers stage 2. The three stages and the applicable guidance are:

Lifecycle Stage	Applicable EU Guidance
1 – Product development	ICH Q8R2
2 – Process validation	This new CHMP guidance
3 – Ongoing process verification	EU GMP Annex 15

The scope of this draft revision covers both human and veterinary medicinal products. It is also applicable to biological products, but these should be considered on a case-by-case basis in view of the complex nature and inherent variability of biological substances. Unlike the FDA guidance, it is NOT applicable to APIs.

Words of Wisdom

"Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives."

William A. Foster

Regulatory
Update

Words of Wisdom

"In order to learn you have to risk change... changing your mind!"

Dwight Frindt

The guidance allows different approaches to process validation: the traditional approach, what it calls "continuous process verification" and a "hybrid approach" of the combination of the two.

The number of batches required for process validation (PV) has been a subject of much debate since the U.S. FDA finalized its PV guidance in January 2011. The revised CHMP guidance states:

> *"The number of batches should be based on the variability of the process, the complexity of the process/product, process knowledge gained during development, supportive data at commercial scale during technology transfer and the overall experience of the manufacturer. Data on a minimum of 3 production scale batches should be submitted unless otherwise justified. Data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches and a justification ..."*

So the EMA appears to still be wedded to the traditional approach and the magic three batches, which is disappointing. The 2011 FDA guidance on process validation moved the whole concept of process validation away from being a one-time event, conducted around the time of submission of the regulatory dossier to obtain a marketing authorization, to a lifecycle process. It would seem that the EU authorities do not understand or share this lifecycle concept as the "traditional" approach, with the unscientific three batches, is still considered acceptable.

The new approach given in section 5.2 of the guidance is called "continuous process verification" and is essentially one part that has become more generally known as the "quality by design" (QbD) approach, following the implementation of ICH Q8.

Section 5.3 is titled "Hybrid approach" and allows for the use of the traditional approach for some steps in a manufacturing process and the continuous process verification approach in others.

Section 5.4 gives requirements for design space verification.

There is also a new section 8 titled "Standard vs. non-standard methods of manufacture."

If you need a more detailed understanding of the modern approach to process validation, including equipment and utility qualification, then our 3.5 day course on this subject in Manchester, UK, from 9 to 12 June will be perfect for you. For details, see http://www.nsf.org/training-education/training-entry/modern-approaches-to-process-validation.

EU GMP Annex 15: Validation

A draft of a revised Annex 15 was published for comment on February 6, 2014. Comments are due by May 31, 2014.

The proposed revision is to take account of ICH Q8, 9 10 and 11; indeed, the draft states in the Principle section at the start of the guide that *"The relevant concepts and guidance presented in ICH Q8, Q10 and Q11 should also be taken into account."*

The section "Qualification stages of equipment, facilities and utilities" has had a section on user requirements specification (URS) added. This was a glaring omission from the 2001 version that has finally been rectified. The URS is an essential starting point because, as the new draft states, *"The URS should be a point of reference throughout the validation life cycle."* This section also has new requirements for factory acceptance testing (FAT) / site acceptance testing (SAT).

The section on process validation makes reference to the CHMP Note for Guidance on Process Validation and uses the same terminology as the 2014 CHMP Guideline on Process Validation to describe traditional and continuous verification approaches to product development. The draft Annex required that *"The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented …"* The validation protocol must define the *"critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on development data or documented process knowledge."*

Products that have been developed by a quality by design approach can follow a continuous process verification approach as an alternative to traditional process validation. A hybrid approach using the traditional approach and continuous process verification for different production steps can also be used.

There is a section that is analogous to stage 3 of the 2011 FDA Guidance on Process Validation, but the FDA description of continued process verification for this stage is replaced by '"ongoing process verification" in the draft Annex 15. Presumably this change of terminology is to avoid confusion with the continuous process verification approach. This section 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."*

There are new sections on verification of transportation, validation of packaging and Validation of utilities. The section on validation of test methods mostly refers just to Chapter 6 of Part 1 of the EU GMP Guide but has some additional requirements for microbial testing.

The revised section on cleaning validation requires that *"Limits for the carryover of product residues should be based on a toxicological evaluation to determine the product specific permitted daily exposure (PDE) value."* This aligns with the draft changes to EU GMP Chapters 3 and 5 and the draft CHMP "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" that was published in January 2013.

Other changes to the cleaning validation section include the need to assess the influence of the storage time before cleaning and the time between cleaning and use, which should be taken into account when defining hold times (dirty and clean) for the cleaning validation. The maximum length of a campaign (in both time and number of batches) should be the basis for cleaning validation exercises.

Revision of EU GMP Chapter 6 – Quality Control

The final version of a revised Chapter 6 was published in late March 2014 and becomes effective on October 1, 2014. The final version is almost identical to the draft revision that was published on January 17, 2013. The revision adds more emphasis on the need to investigate out of specification (OOS) and out of trend (OOT) results. The need for a procedure for OOS/OOT results is added to the documentation section and the requirement that "Any out of trend or out of specification data should be addressed and subject to investigation" is added.

The principal changes introduced by this revision concern requirements for test method validation and transfer; a whole new section, "Technical transfer of testing methods," has been added. The need to verify test methods that were not originally validated by the laboratory using them has been added, as has the requirement for reference standards to be certified, qualified and verified as suitable for the intended use.

There are also some new requirements relating to the use of secondary reference standards, the preparation and verification of culture media, and the control of animals used in testing.

Words of Wisdom

"The risk of a wrong decision is preferable to the terror of indecision."

Maimonides

Words of Wisdom

"It is wise to direct your anger towards problems – not people; to focus your energies on answers - not excuses."

William Arthur Ward

International News

A Global Regulatory Authority?

At a recent conference in London hosted by the UK Medicines and Healthcare products Regulatory Agency (MHRA), US Food and Drug Administration (FDA) Commissioner Margaret Hamburg announced that the FDA and other countries' regulatory authorities are considering forming a global authority, the International Coalition of Medical Regulatory Authorities (ICMRA), to help improve pharmaceutical safety and quality.

The goal of the ICMRA would not be to develop identical standards, but to provide the public with "high-level, strategic advocacy" around quality. Commissioner Hamburg said "It can provide direction for a range of areas and actions that are common to many medical product regulators; identify areas for potential synergies to be made; and, wherever possible, leverage existing efforts to maximize global impact. We must ask ourselves how we can weave our various efforts into a coherent and sustainable global system of governance, oversight and safety."

This idea for ICMRA builds upon the cooperation between the FDA, the European Medicines Agency (EMA), Health Canada, the Therapeutic Goods Administration (TGA) and other regulatory authorities who have already started sharing information from quality inspections of manufacturing facilities.

US News

Draft Analytical Procedures and Methods Validation for Drugs and Biologics

On February 19, 2014, the US FDA issued new draft guidance for industry, Analytical Procedures and Methods Validation for Drugs and Biologics. However, this revised draft guidance does not address specific method validation recommendations for biological and immunochemical assays for characterization and quality control of many drug substances and drug products.

This new draft is designed to complement ICH Q2(R1) and, when approved, will replace both the 2000 draft guidance and the 1987 approved guidance, Submitting Samples and Analytical Data for Methods Validation. It will apply to both drugs and biologicals, but not to INDs/IMPs.

The section Analytical Methods Development emphasizes the need for robustness to be evaluated during the early stages of development. It states that "To fully understand the effect of changes in method parameters on an analytical procedure, you should adopt a systematic approach for method robustness study (e.g., a design of experiments with method parameters). You should begin with an initial risk assessment and follow with multivariate experiments."

The draft guidance lists the essential information you should include in an analytical procedure.

Section V of the draft has requirements for reference standards. Where reference standards are not sourced from official sources (such as pharmacopoeia or CBER for biologics) they should be characterized by procedures including routine and beyond routine release testing. The additional testing could include attributes to determine the suitability of the reference material not necessarily captured by the drug substance or product release tests, e.g. more extensive structural identity and orthogonal techniques for purity and impurities, and biological activity.

For biological reference standards and materials, the draft recommends following a two-tiered approach when qualifying new reference standards to help prevent drift in the quality attributes and provide a long-term link to clinical trial material. A two-tiered approach involves a comparison of each new working reference standard with a primary reference standard so that it is linked to clinical trial material and the current manufacturing process.

Section VI is about analytical method validation in the regulatory submission. The validation characteristics that need to be considered are those defined in ICH Q2(R1). It requires that the results from the robustness evaluation be included in the regulatory submission. If a compendial method is to be registered, it requires that information to demonstrate that the compendial procedures are suitable should be generated under a verification protocol and included in the submission.

Section VIII details the lifecycle management of analytical procedures and part B of this section provides expectations for analytical method comparability studies.

SINGAPORE

A KEY PHARMACEUTICAL HUB

For such a small country, Singapore punches well above its weight in many areas including pharmaceuticals and biotech, with more than 30 of the world's leading biomedical science companies established on the island. NSF Health Sciences continues to support its client base in the region with customized training courses and consulting.

We are also working to establish links with Singapore's Employment Development Board (EDB) to provide high quality training and education for the pharma/biotech sector. EDB and NSF Health Sciences share a common passion, to provide our industry with a well-educated and informed workforce at every level. We also hope to strengthen our team of associates and consultants in the region so we can continue to support companies in Singapore and the Asia Pacific region. If you have colleagues and affiliates in the region, tell them to look out for us.

UTRECHT

A JOINT SEMINAR WITH DERKS & DERKS BV

At the end of March, NSF Health Sciences Pharma Biotech ran a joint seminar in Utrecht with a Netherlands-based consulting company, Derks & Derks BV, involved in a QP support role. The seminar included an essential two-hour legislation update from NSF instructor Peter Gough and a very innovative approach to managing change presented by Jan Derks.

The seminar was hosted by Mike Halliday of NSF Health Sciences and was a huge success. Almost 70 delegates attended and many decided to follow up with further training, auditing or consulting from NSF experts after the course. It was a pleasure to meet so many familiar and new faces in the joint seminar with a very informative exchange and a great atmosphere of fun and education.

It was such a successful support for the pharma industry that plans are already being made to repeat the experience.

NSF Health Sciences Pharma Biotech People...

Words of Wisdom

"Often the difference between a successful person and a failure is not one has better abilities or ideas, but the courage that one has to bet on one's ideas, to take a calculated risk – and to act."

Maxwell Maltz

George Toscano

George Toscano is the Senior Director of Quality Systems at NSF Health Sciences Pharma Biotech, based in Washington, DC

George Toscano joined NSF last September and has extensive experience assisting pharmaceutical and biologics companies. He has served as project lead and expert consultant on compliance initiatives involving corporate 483 responses, warning letters, consent decrees, application integrity policies (AIP) and import alerts.

His technical background includes validation, vendor qualification, auditing, batch record review, product release and stability, investigation of non-conformances and cGMP (current Good Manufacturing Practice) and GLP (Good Laboratory Practice) training. He has provided hundreds of companies with expert counsel on laboratory and manufacturing investigations, CAPA (corrective and preventative action) development and implementation, training, stability programs and the implementation of quality systems.

George is a recognized data integrity expert who can offer advice on developing robust quality systems to ensure data is accurate and reliable. He conducts audits and assessments and provides companies with compliant and practical quality and regulatory strategies to achieve compliance.

George's personable nature and his ability to engage with all levels of management in an organization have proven essential to achieving lasting improvements.

"I take pride in not only helping companies identify their deficiencies, but in developing and implementing practical and sustainable solutions," he says. "To make these solutions last, I seek company engagement at all levels to have the organization own and embrace the solution."

Luba Skibo

Luba Skibo is an Executive Director at NSF Health Sciences Pharma Biotech, based in Boston, MA

Luba joined NSF last January and has over 20 years of pharmaceutical industry experience including 14 years of regulatory, CMC and quality operations experience. She has held industry positions from R&D Scientist and QC Laboratory Supervisor to Head of Worldwide Regulatory Operations and Head of Regulatory Affairs.

Luba has an in-depth understanding of US and EU pharmaceutical law with strategic and hands-on experience with NDA, BLA and MAA filings as well as management of global post-approval changes.

Emerging markets and the geographical extension of products are areas of expertise and passion. She conducts a number of training events on a variety of topics including emerging markets regulatory framework, logistics and cultural sensitivities.

Luba has an established record of direct interactions and successful negotiations with FDA and other health authorities on new product filing strategies, labeling and site transfers. This would not have been successful without a thorough understanding of GLP, GMP and GCP. Luba provides training on pharmaceutical quality system design, change control system design, global GMPs and integration of complete product life cycle management. She conducts REMS and GMP audits as well as due diligence assessments for quality and regulatory affairs aspects of the business.

Luba has a very personable interactive style of training and a thorough understanding of different cultures on a personal level. She offers training and consulting services in Russian and Spanish as well as English.

She believes that in today's global environment, helping to ingrain quality and "right first time" at an individual level is the best way to ensure safe and quality medicines are delivered to the end user.

NSF Health Sciences

YOUR FOURTH EMERGENCY SERVICE: SUSTAINABLE REMEDIATION

In an ever-changing world even the best can take their eye off the ball and, before they know it, get into regulatory trouble. Remember our article on complacency (page 6)…it can be the enemy from within! If this happens, please remember we are here to help. We have considerable success helping clients in pharmaceuticals, biotech and medical devices through very difficult times. Whether it be consent decrees, warning letters, importation alerts, Inspection Action Group (IAG) remediation or WHO "decertification," we can help. What we do and how we do it are driven by our CORE BELIEFS:

We cultivate partners, not clients

- We want to cultivate a lasting relationship based on mutual respect and "return on investment." In short, we will stick with you no matter what
- Our team members are some of the best available. Most have in excess of 30 years' hands-on experience. They are seasoned professionals who have walked in your shoes

We are driven by YOUR SUSTAINABILITY

- We don't believe in quick fixes
- We believe success depends on what you STOP doing. Disaster awaits those who try to do everything… and do nothing properly
- We work with you to identify and implement simple and sustainable solutions. We believe introducing unworkable levels of complexity is wrong. We are driven by helping you identify and implement SIMPLE, practical and sustainable solutions
- As painful as remediation can be, we believe that it must be used as an opportunity to change mind-sets and culture, simplify systems and procedures, and improve business performance. Our objective is to leave you better off than when we found you!

We help you CHANGE YOUR CULTURE

- You can't change culture without changing the way people think
- Our customized approach to education (using the 10/20/70 approach as described on page 9) will help change attitudes and behaviors in the workplace
- Our workplace coaching and mentoring programs, combined with our customized education workshops, focus on your people, your products, your processes and your systems
- Our unique approach to education is designed to improve skills in areas vital to your long-term success such as decision making, problem solving, change management, error reduction, quality ownership, leadership behaviors and more
- In short, we leave your people better informed and educated, and equipped with the skills needed to take your business to the next level

We help our partners plan for the future, not the past; to think beyond remediation

- Even in the thick of remediation, we believe in solutions fit for the future, not the past
- Our excellent connections with industry and regulators mean that the advice we provide is current and reflects best-in-class practices
- We will help you set standards that are fit for purpose, based on your ways of working and good science and common sense, not ones that are over complicated and unattainable

We are driven by you getting a "return on investment"

- After remediation has been completed, we don't abandon you. We stay in contact, either by phone, face to face or by email. Whatever it takes. Remember, we focus on building lasting relationships
- We get immense satisfaction when our clients tell us that the regulatory action and remediation have improved their business by allowing them to create simpler systems, robust processes, and better educated and more motivated people

So, when faced with the threat of regulatory action, please give us a call at **+1 857-277-0060** in the US or **+44 (0)1751 432999** in Europe. We have the right people, driven by the right beliefs, to provide the solutions you need…the first time.

Forthcoming Courses

What's planned for July – October 2014

Pharmaceutical GMP Laws and Guidance

Boston Marriott Cambridge, Cambridge, MA, USA

July 15-17

This course will provide a comprehensive review and analysis of pharmaceutical GMP requirements globally, including the roles of ICH, PIC/S, and pharmacopoeias. The course will deepen your knowledge of the pharmaceutical regulatory environment and keep you up-to-date with the latest developments and trends in the pharmaceutical industry related to regulations, guidances and inspections. It is a cornerstone course of our modular educational program and a key knowledge requisite for quality leaders and technical professionals. If you are ready to deep dive into the pharma regulatory environment and want to stay abreast of the latest regulatory developments, this course is for you!

Course Fee: $2,950

The Role & Professional Duties of the Qualified Person

Hilton York Hotel, York, UK

July 21-24

The principal objective of this course is to emphasize how the QP should conduct themselves in discharging their legal duties. The role and duties of the QP are constantly being added to and it is essential that QPs keep up-to-date with new expectations. This course covers these new challenges in detail to help you understand them and their impact. Also included is a simulation of a typical UK QP interview as conducted by the three professional bodies.

Course Fee: £2,560 ex VAT

Excipient Risk Analysis and Auditing

NSF Health Sciences, Boston, MA, USA

July 22-23

This course will review recent legislation enacted by key regulatory bodies including EMA, FDA, CFDA, ANVISA to ensure excipients are produced and supplied according to Good Manufacturing Practice. The impact on excipient manufacturers, brokers and distributors will be reviewed along with the expectations of drug product license holders. This course will explain expectations for excipient risk analysis and how to adapt your company's Vendor Management Program accordingly. The pharmaceutical industry often accounts for only a small proportion of an excipient manufacturer's volume and often auditors need to work around time constraints. This course will cover good auditing techniques and strategies to overcome these constraints while meeting your company's objectives.

Course Fee: $1,775

Effective Pharmaceutical Quality Management Systems

Boston Marriott Cambridge, Cambridge, MA, USA

August 5-7

This course will provide a blueprint for a phased approach to quality management systems and will cover:

- The philosophy and practice of QA, GMP and QC throughout the product lifecycle
- The essential elements of an effective quality management system based on ICH Q10 Pharmaceutical Quality Systems
- How firms use QbD, Knowledge Management, and Risk-Based Decision Making in development
- The importance of change management during R&D
- Why knowledge management is an essential enabler of an effective quality system
- Making effective use of contract manufacturing and testing

Course Fee: $2,950

*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

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NSF reserves the right to make any changes which may become necessary.

NSF Health Sciences Pharma Biotech

Establishing a Sustainable Quality Culture

WORK SHOP

NSF Health Sciences, Boston, MA, USA

August 8

While ICH Q10 does not explicitly mention "Quality Culture" it is clear that without this, the principles of Q10 will NEVER take root in a company. The quality culture is measurable and companies range from Quality Mindset "Firmly Embedded" to "Not Embedded at All ". The very best companies are never complacent and continually take action and make decisions which reinforce their values and further embed the quality mindset across the organization.

This workshop will review actions/strategies companies are following to embed a quality mindset across the organization and we will cover methods used to evaluate the quality mindset and leadership of CMOs, CROs, and suppliers.

Course Fee: $500

Deviation and CAPA Systems – Best Practices

Amsterdam Marriott Hotel, Amsterdam, The Netherlands

September 1-2

How good is your Deviation and CAPA system… or are you at RISK? In this course you will learn:

- How to use your deviations to drive down costs and reduce complexity by removing non-value-adding activities and driving forward Continuous Quality Improvement
- How to make 'repeat' incidents a thing of the past!
- How to apply structured, risk-based decision making tools and techniques to ensure that every incident is investigated to root cause in a consistent and thorough manner
- How to report, investigate and resolve incidents within hours, not days or weeks
- How to 'triage' or prioritize deviations so that you focus your time and resources on what really matters
- How to make sure that your deviation reports provide an accurate history of events!!

Course Fee: £1,470 ex VAT

Human Error Prevention

Amsterdam Marriott Hotel, Amsterdam, The Netherlands

September 3-5

If you think human error is the real cause of your quality problems then think again! It isn't. Human error is only the symptom, never the cause. You will leave the course with the tools and technique needed to reduce errors, protect your business and drive continuous improvement.

Course Fee: £1,910 ex VAT

Active Pharmaceutical Ingredients

QP

Newcastle Marriott Hotel Gosforth Park, Newcastle, UK

September 8-11

The quality of a medicine depends in no small part on the quality of its ingredients, and in particular, the active. Thus, the QP and other key professionals must have a thorough understanding of how the manufacture and control of the active and its supply chain may influence the fitness for use of the finished product.

This course, to include visits to API manufacturing facilities, is designed to provide you with this.

Course Fee: £2,560 ex VAT

How to Audit – Chemical API

Newcastle Marriott Hotel Gosforth Park, Newcastle, UK

September 12

Improve your knowledge in the area of API auditing, to include standards used and industry norms applied.

This course will also help you to:

- Improve skills in preparing for API audits
- Increase confidence in conducting API audits
- Understand how to report observations and respond to corrective action plans
- Develop tools needed to cover specific areas within the audit

Course Fee: £735 ex VAT

Book your place at www.nsf.org/info/pharma-training

Forthcoming Courses

What's planned for July – October 2014

How to Audit – Key Excipients

Newcastle Marriott Hotel Gosforth Park, Newcastle, UK

September 12

New directives and expectations place increasing pressures on companies to audit the entire supply chain of starting materials including excipients.

This course is designed to provide practical help and guidance to those engaged in the auditing of excipients.

Course Fee: £735 ex VAT

Cleaning Validation

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

September 9-10

Practical advice on how to design and execute cleaning validation studies to meet current regulatory expectations in a cost-effective way. General principles of cleaning validation will be supplemented by specific case studies from industry specialists, and the special challenges of clinical trials manufacture and packing will also be covered in detail.

Course Fee: £1,470 ex VAT

Pharmaceutical GMP

Hilton Dublin Hotel, Dublin, Ireland

September 15-18

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'.

- Why we have GMP
- EudraLex Volume 4
- A clear comparison of EU and FDA GMP requirements
- New GMP initiatives and regulations
- Practical advice on dealing with the 'difficult areas' of GMP
- How GMP is influenced by the 5 P's
- A panel discussion session to explore YOUR specific GMP problems

Course Fee: £2,550 ex VAT

Human Error Prevention and Reduction

NSF Health Sciences, Boston, MA, USA

September 16-17

We have been teaching human error prevention for over five years, touching delegates from over 200 companies including regulatory agency representatives in Europe and the USA.

The training in human error reduction is a core component of our human reliability program and includes three primary elements: the science of human error, investigative techniques for error avoidance and proactive approaches for error avoidance.

This two-day course will help you and your staff see human error from an entirely different point of view, and provide you tools and techniques that will make a difference back at your site.

Course Fee: $1,775

Effective Pharmaceutical Audits and Self-Inspections

IRCA CERTIFIED TRAINING COURSE A17638

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

York Marriott Hotel, York, UK

September 22-26

Pressure on the pharmaceutical industry to audit has never been higher and continues to increase. Supply chain decisions and batch release decisions are being made based on audits and self-inspections. As a result, a high level of scrutiny is being placed on the training and development of auditors and self-inspectors.

This course will provide delegates with education, training and development to meet today's pharmaceutical pressures, including the auditor skills and toolbox of auditing techniques needed by the successful pharmaceutical lead auditor.

This course meets the training requirements for the new IRCA (www.irca.org) Certification of Pharmaceutical Quality Management Systems Auditor/Lead Auditor (PQMS).

Course Fee: £2,750 ex VAT

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

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NSF reserves the right to make any changes which may become necessary.

NSF Health Sciences Pharma Biotech

Analyzing and Trending Data

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

September 23-24

The ability to trend and analyze data is now an essential survival skill and this pharmaceutical training course will show you how to do this simply and effectively.

We will provide you with the understanding of several fundamental statistical tools for analyzing data and enable you to understand what the output from these tools is telling you about your product or process. This, in turn, will give you powerful information that you can use to provide continuous trending and to drive quality improvement.

Course Fee: £1,470 ex VAT

Risk-Based Decision Making for Quality Professionals and QPs

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

September 23-24

The manufacture of medicines is easy – until something goes wrong. Important decisions have to be made quickly and these are rarely simple. There is never enough time, and important data and information are usually in short supply.

To protect your patients and your reputation your decisions must be:

- Scientifically justified
- Based on an objective and realistic assessment of RISK
- In compliance with regulatory requirements and expectations
- GOOD for your business!

This course will provide you with the tools and techniques to make the right risk-based decision no matter how challenging the situation. It is not what you know that matters – it is what you do with what you know.

Course Fee: £1,470 ex VAT

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

A-Z of Sterile Products Manufacture

Amsterdam Marriott Hotel, Amsterdam, The Netherlands

September 29 – October 2

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 the US FDA's industry guidance, 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: £2,550 ex VAT

EU New Proposed Chapters

WEBINAR

10am EST

October 2

Proposed and recently implemented changes to the EU GMPs (EudraLex Volume 4 Part 1) are reviewed in detail; changes to both Chapters 1 to 9 and the Annexes will be covered. This will include the potential implications of these changes for pharmaceutical manufacturers.

Course Fee: $100

Pharmaceutical Law & Administration

QP

York Marriott Hotel, York, UK

October 6-10

A thorough understanding of the laws and legal process within Europe and beyond is essential knowledge for all QPs, and this is equally true for other pharmaceutical technical managers. In this course you will learn:

- 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 QP
- The UK medicines legislative framework
- US and other international pharma legislation
- Other relevant laws and guidelines

Course Fee: £3,350 ex VAT

Book your place at www.nsf.org/info/pharma-training

Forthcoming Courses

What's planned for July – October 2014

Free Seminar for Prospective QPs and Sponsors

York Marriott Hotel, York, UK

October 7

Since 1990, we have collaborated with the University of Strathclyde 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 this free seminar 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

Course Fee: FREE

Pharmaceutical Regulatory and Quality Management for Emerging Markets

JW Marriott Washington, Washington, DC, USA

October 7-8

The pharmaceutical market in the emerging markets is anticipated to continue to growth at 7-10% rate over the next 3-5 years. Therefore, understanding BRIC markets is of fundamental importance to managers and leaders in pharma companies today.

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. The pace of change in these regions is impressive. Regulatory requirements for conducting clinical studies and commercializing drug products in these regions continue to shift frequently with unique local requirements. Being informed is being prepared and this course is designed to keep you informed.

Course Fee: $1,775

GMP for Clinical Trials Manufacture and Supply

Park Hotel Amsterdam, Amsterdam, The Netherlands

October 13-16

Questions such as:

- Does the FMD 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 CT regulation in 2016?

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

Course Fee: £2,550 ex VAT

Pharmaceutical Legislation Update

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

October 21

The Qualified Person and other technical personnel need to be informed and aware of pharmaceutical legislation. Changes in legislation and guidelines, and their interpretation, can have significant implications for the individual and the 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: £735 ex VAT

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

Course details and prices 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.

NSF Health Sciences Pharma Biotech

How to Perform Effective Product Quality Reviews

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

October 22

On 1 January 2006 the EU implemented a change to Chapter 1 of the EU GMP Guide to add the requirement to produce a regular PQR. The FDA has long required product reports to be submitted for licensed products, and ICH Q7 also requires that "processes should be periodically evaluated to verify that they are still operating in a valid manner".

This course is designed to assist you and your company in producing PQRs which meet these GMP expectations in an efficient manner that will add VALUE to your business as well as compliance to your operations.

Course Fee: £735 ex VAT

Good Autoclave Practice

TBC, London, UK

October 22-24

A comprehensive course on the practicalities of…

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

Course Fee: £1,910 ex VAT

Ongoing Stability Testing

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

October 23

In June 2006 the EU implemented a change to Chapter 6 of the EU GMP Guide to add the requirement that the stability of marketed products be monitored according to a continuous programme that will detect any stability issues. ICH QP GMP for APIs also requires that "at least one batch per year of API manufactured should be added to the stability monitoring programme and tested annually to confirm stability". This course is designed to help you understand and meet the relevant EU GMP expectations in an effective and efficient manner that will add value to your business.

Course Fee: £735 ex VAT

NSF's OTC GMP Program: What It Is and How to Use It

WEBINAR FREE SEMINAR

10am EST

October 23

Over the Counter drug manufacturers have been cited in recent years for significant compliance failures. A number of companies have managed product recalls and suffered a rapid loss of confidence by both customers and regulators, and it will take these companies years to recover. The FDA 483 observations cited by the agency cover Quality Systems, Procedures, Specifications and a long list of other weaknesses. The majority of the issues cited by the agency can be avoided if companies pursue a proactive, forwarding-thinking strategy of compliance. NSF has developed a program to help OTC manufacturers identify compliance gaps and develop improvement plans, and provide training to manufacturers of OTC products to help them comply with regulations.

Course Fee: FREE

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

Book your place at www.nsf.org/info/pharma-training

NSF Health Sciences Pharma Biotech

Formerly NSF-DBA

Our Core Beliefs: When We Work with You We…

1) **Cultivate long term relationships**.
2) Help you become more **sustainable.**
3) Provide you with **education**, not training.
4) Help you **plan** for the future, not the past.
5) Help you challenge the status quo and **think differently.**
6) Ensure you get a **return on investment.**

www.nsf.org/info/pharmabiotech

NSF Health Sciences Pharma Biotech

Formerly NSF-DBA

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