

Journal

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**GET RISK
READY
FOR 2018**



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welcome

Welcome to the first edition of 2018! Our theme is **RISK**. One of our clients was faced with the challenge of stripping out cost without compromising compliance. A culture of risk aversion had created an unworkable level of complexity that was no longer sustainable. That's right; their risk aversion had actually created greater risk. Sound familiar? We must all remember that risk aversion is bad for business in many ways:

- > Chasing the "zero risk" game smothers creative and critical thinking at a time we need them most.
- > Risk aversion creates the dangerous illusion of certainty when there is none.
- > Risk aversion adds complexity when brutal simplification is vital.

The crux is this. The urge toward safety can be good, but if left unchecked, it can lead to disaster. *We think many companies have gone too far. We think the key to your success is to become less risk averse and more risk smart.* This means making tough choices. Please don't forget we are here to help. If you want to move away from reactive risk assessments to proactive risk management, or need to strip out cost without compromising compliance, we can help you become risk smart!



Martin Lush



Martin Lush,
Global Vice President, Pharma
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Is Fear of Risk Your Biggest Risk?



by Martin Lush,
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Why Becoming More *Risk Literate* Is So Vital

Let's start with an exercise in risk-based decision making. Imagine I'm standing in front of you with £50. You can take it now (a low risk, sure bet decision) or double your money at the toss of a coin (but stand the chance of losing it all). Heads you win £100, tails you leave empty handed. What would you do? What is your risk threshold? Most would probably take the £50. After all, losses loom larger than gains and most people are risk averse. However, in a volatile and uncertain world, playing safe is the riskier option! Even maintaining the status quo is dangerous.

"The biggest risk is not taking any risk. In a world that's changing really quickly, the only strategy that is guaranteed to fail is not taking risks." Mark Zuckerberg

The pharma industry has always been risk averse. After all, mistakes can cost lives. But have we gone too far? I believe we have. Do we need to rethink our relationship with risk? I think we do. Is ICH Q9 (Quality Risk Management) fit for purpose or is it just poorly applied?

A quiz to get you thinking. Answer the following with a simple yes or no:

1. Does your company take a zero-risk approach to most things?
2. Is risk defined as the consequence of severity of harm, probability of occurrence and likelihood of detection?
3. When taking steps to reduce risk, do you habitually add more? It's what I call the "just in case" approach to risk mitigation. More checks, more double signatures, more detailed instructions, more discussions and more measures? More complexity in general... just in case.
4. When faced with risks, are you guilty of paralysis by analysis? Do you overthink?
5. Is failure mode effect analysis your main risk assessment tool?
6. Do you typically err on the safe side when things go wrong?



If you have more yes than no answers, you need to rethink your attitude to risk and its management. I'm not saying take more risks. What I am promoting is being more risk smart. In one sense the urge toward safety can be, and is, good; but if left unchecked can lead to disaster.

But risk aversion is not just natural, it's attractive because it's easy. But, there is a price to pay:

- > Risk aversion creates the dangerous illusion of certainty when there is none. We need to remind ourselves of Franklin's Law:
"Nothing is certain but death and taxes."
- > Habitually failing safe kills the creativity and critical thinking skills we need to navigate an uncertain world.
- > Risk aversion adds complexity and confusion at a time when simplicity and clarity are vital.
- > Risk aversion slows innovation and improvements when we need them most. Being risk smart acknowledges uncertainty rather than ignoring it. In times of massive uncertainty, we will have some very tough choices to make. We can only make important decisions if we are risk smart.

Your Call to Action: Five Steps to Becoming Risk Smart

1. Stop defining risk in terms of severity of harm and probability of occurrence.

This implies risk is painful, dangerous and something to be avoided. As leaders you must feel safe with risk. View risk as managing and being comfortable with uncertainty (variability).

Is ICH Q9 fit for purpose?

To recommend deleting severity of harm and probability of occurrence from our risk vocabulary sounds like I'm questioning the value of ICH Q9. I actually like ICH Q9. It's logical and pretty straightforward, but it is far from state-of-the-art. I think we need to revisit it and ask some critical questions with one objective in mind; improvement.

- > Why has ICH Q9 been so poorly applied across our industry?
- > Why is ICH Q9 typically used reactively rather than proactively?
- > How can we use any risk management process without in-depth understanding of our products and process, probability and frequencies?
- > How can the process be improved using all the latest research and best practices relating to the psychology of risk, risk-based decision making and the use of big data for risk profiling?

...so, let's start the discussion!

2. Ban the term zero risk and replace it with risk smart.

Zero risk is a dangerous illusion. It doesn't exist. Remember the role intelligent risk management has played in every human advance. Remember, being risk smart doesn't mean gambling with patient safety. It's just a trigger to remind us of reality. Risk is everywhere - in every decision we make and in every problem we solve. Risk smart companies will succeed. Those trapped by institutional risk aversion will not. Leaders at every level must feel safe with risk.

3. Recognize that risk-based decision making is a skill that can be taught, practiced and perfected.

Remember that risk management and making risk smart decisions is about making decisions under uncertainty. Don't worry about the decision; just focus on driving down uncertainty. To develop and refine your risk-based decision making skills, visit our resource library or follow these links:

- > NSF's Six to Fix Video: Decision Making Under Pressure, Part 1
- > NSF's Six to Fix Video: Decision Making Under Pressure, Part 2
- > Webinar: Judgement Calls – Making Decisions Under Pressure
- > Webinar: Risk Management – Best Industry Practices

4. Create a culture that allows you to fail fast.

An open-loop culture uses problems, errors and mistakes to drive continuous improvement. When the opposite happens and problems and errors are considered bad news, a risk averse, toxic blame culture follows.

5. Educate, educate, educate.

To become risk smart, profound knowledge of the psychology of risk aversion, the science of risk-based decision making and (importantly) probabilities is essential. When faced with assessing risk, numbers can help navigate the wash of sentiment that often leads to a risk adverse decision. Numbers, in the form of probability, can offer a kind of life raft from which to make informed, risk smart decisions. Acquiring some level of statistical literacy is a vital component to risk smart decisions.

Here is your reading list to improve your risk literacy:

- > Risk Strategy: Understanding Risk to Improve Strategic Decisions by Jamie MacAlister
- > Reckoning with Risk: Learning to Live with Uncertainty by Gerd Gigerenzer
- > Risk Savvy: How to Make Good Decisions by Gerd Gigerenzer
- > Risk Intelligence: How to Live with Uncertainty by Dylan Evans

A new acronym has entered the Oxford English Dictionary: VUCA. We all live in a volatile, uncertain, complex and ambiguous world where only the risk smart will prosper. We have limited resources so we have to make tough choices. In the final analysis, success awaits those who have the courage to do only what is right. This means making only risk smart decisions.

What Does the Future Hold for Risk Management in the Pharma Industry?

We don't need to reinvent the wheel just humbly borrow from those who already have the solutions, such as the financial and insurance sectors. I was speaking with a good friend who works as an actuary for an insurance company that specializes in insuring pharma companies. They feed all of their clients' risk factors into an algorithm to generate a risk profile. Their insurance premium then reflects their risk profile, providing some financial protection following catastrophic failures or losses. We need to do the same, but with a focus on prevention. Repeat deviations, customer complaints, yield losses, reconciliation failures, plant utilization, staff turnover, number of full time employees vs. contractors, supply chain complexity and lots more are all risk factors that can be quantified and used to make better risk smart decisions focussed on prevention, not reaction.



If you want more information, just drop us a line at pharmamail@nsf.org. Or visit our resource library www.nsf.org/info/pblibrary to access a wide range of useful resources.



by Andy Barnett,
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Risk Assessment: A CLOSER LOOK

We are all aware of the heightened emphasis the FDA is placing on risk assessment. ICH Q9, Quality Risk Management was adopted by the FDA in June 2006. You might expect, after 11 years, the industry would be fully on board with the practices recommended in this document, but we may not have come as far as one might think in the area of risk estimation.

The two primary principles of quality risk management, per ICH Q9, are:

- > *The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient*
- > *The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk*

My first takeaway from these two expectations is that investigation reports should always include at least one or two sentences that explicitly describe the risk that the non-conformance may have on the patient, focused on the severity of the risk. If the non-conformance was not detected or escaped the containment system, would the patient be injured? Many non-conformances pose little risk. This does not absolve you of the obligation to discuss the risk. If the risk is low, say so! Just be sure to justify your decision.

My second takeaway based on the second bullet is that the level of effort should be commensurate with the level of risk. This is the focus of this article.

Risk assessment (or risk *estimation*) is the key.

- > Do you have an objective, repeatable system to estimate risk?
- > Do you prioritize these risks?
- > Does your investigation SOP require a higher level of due diligence for non-conformances with higher risk?

ICH Q9 has a number of suggested tools for risk management. The most widely used tool is based on the scoring system used in failure mode and effects analysis (FMEA). Each non-conformance is evaluated for severity, occurrence and detection (The acronym SOD may help you remember these three categories). After assigning a risk score for each category, the numbers are multiplied to calculate an overall risk score, called a risk priority number (RPN). The higher the number, the greater the risk.

Many FDA-regulated companies have adopted a three-point rating scale for each category. For those of you who prefer words over numbers, the scores correspond to low, medium or high risk. The purpose of the risk prioritization is to discriminate between risk levels and ensure that higher risk events are subject to a higher standard of due diligence. But, as we will see below, your scoring practices may not deliver the expected results.

First, let's consider the three-point scale used by most facilities. The table below (*figure 1.*)

RPN COMBINATIONS																											
SEVERITY	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3
OCCURRENCE	1	1	1	2	2	2	3	3	3	1	1	1	2	2	2	3	3	3	1	1	1	2	2	2	3	3	3
DETECTION	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
RPN	1	2	3	2	4	6	3	6	9	2	4	6	4	8	12	6	12	18	3	6	9	6	12	18	9	18	27

figure 1.

shows all possible combinations of risk scores and the resulting RPN numbers:

If you examine the RPN column, you will notice that the numbers 1 and 27 only appear one time. The number 2 appears three times. The number 6 appears most frequently – six times! The combinations of risk scores do not result in a nice, linear, continuous scale. Did you notice that there are no RPN scores between 18 and 27? The distribution is shown in *figure 2*.

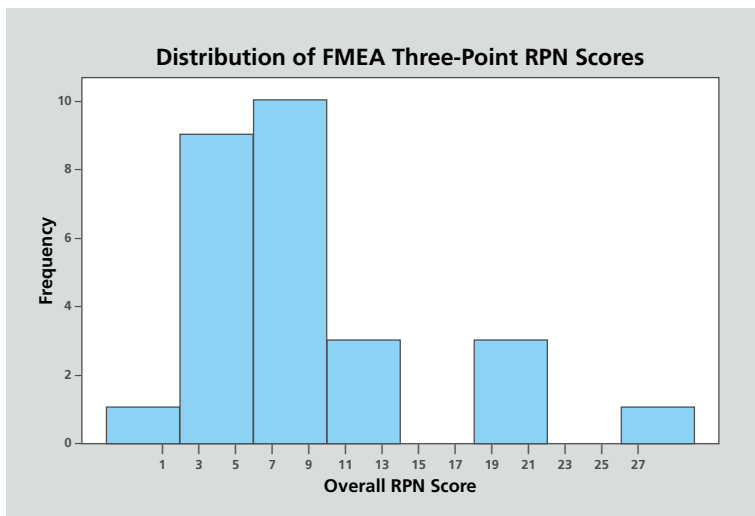


figure 2.

Why is this so important? Because if you do not understand how the RPN scoring system works, you may not discriminate properly.

Many companies assume that dividing the RPN scale into equal segments such as 1-9, 10-18 and 19-27 is sufficient. Think again! If you do this, 74 percent of the possible scores will fall into the low risk category, 22 percent will be medium risk, and less than 4 percent will be high risk. But that is not the end of the story. People have a natural tendency to minimize the scores to lower the overall risk. For example, they will discount severity based on their perception that the detection/containment system is robust. An example: "Although a patient could be injured, the risk is low because we have 100 percent automated inspection".

When I teach risk management courses, I always advise participants to evaluate each category *independently* of one another. This is the only way to ensure integrity when estimating risk.

We recommend that you evaluate your scoring system, including the scoring thresholds

between risk categories. The review should also consider the scoring practices of your employees. Do they discount the risk when documenting the RPN numbers? Look at a large sample of investigations (at least 100) to see how many investigations fall into each category. The breakdown for one client was 95 percent low, 4.5 percent medium and 0.5 percent high risk. If everything is low risk, then you are short-circuiting the intent of the risk assessment process.

Keep in mind that you cannot ignore non-conformances just because they are low risk. This is especially true for repetitive non-conformances. Eventually, management must override the RPN system and insist upon a thorough investigation for repetitive failures. This should be done during quarterly management reviews.

Some people believe they can improve the scoring system by using weighted scores for severity (3, 6 or 9) and regular scores (1, 2 or 3) for occurrence and detection. Such a scheme, while perhaps well intentioned, does not change the ability of the scoring system to improve discrimination. The revised scheme has exactly the same number and percentages of unique RPN numbers. The only way to improve discrimination is to change from a three-point scale to a five-point scale. Just be prepared to spend some time developing definitions and examples of each point on the scale. We think a three-point scale is sufficient, as long as you understand and avoid the pitfalls.

Have a question on this article? Contact us at USpharma@nsf.org.





by John Johnson,
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How the Mighty Fall?

Everything comes to an end someday. Everything all around us follows an organic curve that kicks off with a beautiful idea, a reaction and a spark of energy that leads to conception of a new entity. A business anywhere in the world begins with a promise, a vision and a service or product that is considered valuable or better still, unique. This quantum of energy is at the heart of every living thing.

At first, growth is slow. Ideas and information come and go until, suddenly, everything launches forward into a period of rapid growth, often chaotic and uncontrolled. This can be a fabulously exciting time, full of learning, adrenaline, glories and disasters, and if businesses can survive the initial phase of chaotic growth (adding systems, processes, expertise and assets to their business along the way), growth can be very rapid. This is a heady time for a small business and it can seem like the product or service can do no wrong, with demand exceeding supply. This is a hugely profitable time for any business.

In time though, unless the leading indicators that follow are carefully pre-empted and tackled, a toxic, debilitating virus can slowly take hold of the organization. That virus is **complacency** and it is fueled by an aversion to risk and, unchecked, it can rapidly cause inertia and resistance to change. It is at this point that the organic growth of a company can flatten and move quickly into decline and ultimately to irrelevance. This is the organic lifecycle of any living organism and it has so many parallels in business.

When you consider organizations that have grown rapidly, dominated their field and then (at least to the casual observer) inexplicably deteriorated in performance – the list is large.

It includes:

- > IBM
- > Hoover
- > Imperial Chemical Industries
- > A variety of pharma companies from the 1980s onwards

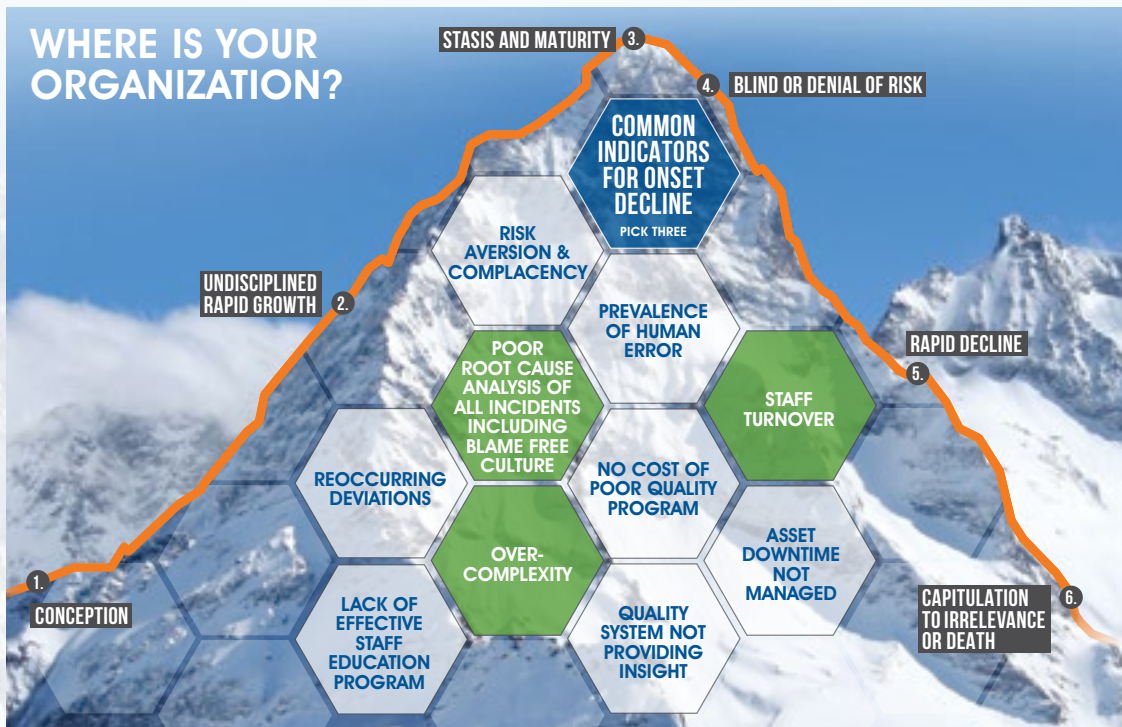
SO WHY DID THIS HAPPEN?

Why couldn't these organizations sustain their growth indefinitely? Why did they reach maturity and then allow competitors to dominate them, allowing their business to wither on the world stage?

Martin Lush, NSF International's Global Vice President of Pharma Biotech and Medical Devices, and I explored the reasons for the onset of demise at the Pharma Integrates conference in London, November 2017, and we asked attendees three key questions:

- > Where are you personally on the organic curve; what are you doing to push back your decline?
- > Where is your organization on the curve; what is it doing to reinvent itself and ensure it stays in the zone of rapid growth for as long as possible?
- > From your experience, what do you see as the top three leading indicators that suggest decline is around the corner?

And the results/three leading indicators are highlighted in green on the graphic below:



The top messages coming back from these industry experts were:

- > Overcomplexity kills business insidiously by strangling innovation, feeding non-compliance and switching off employees.
- > Poor root cause analysis of issues prevents effective CAPA from being put in place; not just risking expensive recurrence and sapping trust and reputation from the company, but also wasting hard-earned revenue in misplaced projects and remediation.
- > Staff turnover is a key indicator that the pharma quality system is not working well, disengaging key experts and making them want to take their experience elsewhere. It is imperative to keep your best people engaged in the business. Switch them off and they go elsewhere.

THE KEY MESSAGES FOR SENIOR MANAGERS ARE:

- > As part of your management review process, an awareness of these leading indicators and a constant willingness to tackle areas of concern is absolutely critical.
- > Studying how other firms thrive in a hard business environment is so important when seeking to change culture, refreshing the quality system or changing behaviors. Learning from the best means “every day is a school day.”
- > We are not here to maintain the status quo, as stasis and complacency bring the onset of decline forward extremely rapidly.
- > Developing a “why/why not” culture, which allows staff to challenge the norms and helps them to seek a deep understanding of their roles in the greater scheme of the company, can only promote a change culture. It also feeds a willingness to seek breakthroughs and a desire to keep learning.

Dinosaurs didn’t evolve quickly enough – make sure your firm is not turning into a tyrannosaurus rex!

AGING FACILITIES



by Nicholas Markel,
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***Aging facilities* is a trendy catchphrase that has taken hold in the biopharmaceutical industry the past few years. While most of us understand intuitively what the words mean, it might be more difficult to identify if age has indeed caught up to your facility and if so, what, if anything, can be done about it.**

Let's face it, age is a universal fact that happens to everyone and everything. You may be one of the privileged few that started in the industry 25+ years ago and have been lucky enough to design, build, commission, qualify and operate new state-of-the-art facilities. It might be painful for you to realize that all of a sudden your baby may now officially be considered an aging facility. While we all recognize that aging is natural, we may not always accept that our beloved baby has aged. Just like people, as facilities age they likely need a bit more maintenance than they did when they were young.

AGE IS ONLY A NUMBER

Just because your facility is old doesn't necessarily mean it's aging and furthermore, to date, no regulatory inspection report has cited aging facility as an issue. So, how can you tell if you have an aging facility? This question is often answered by indirect indicators. Ask yourself some of these questions and if the answers are overwhelmingly yes, then you may have issues which need to be addressed.

- > Do clients, customers or regulators inquire about your capital improvement plans?
- > Is attention being paid to maintenance metrics like breakdown rates?
- > Are your flows atypical? For example, do personnel, materials and waste enter and exit through the same airlock and you find yourself implementing temporal solutions?
- > Do you find "glitter" when wiping your stainless-steel finishes with a finger or paper towel?
- > Do your process demands outstrip your water supply?

- > Do you find yourself turning to places like eBay to keep your equipment running?
- > Does your automation not have audit trail functionality?
- > Do you find yourself having to decrease the amount of time between events like preventive maintenance and requalification?
- > Does your budget for equipment maintenance and spare parts increase year after year?

GREAT! MY FACILITY IS AGING. NOW WHAT?

The industry as a whole is struggling with this question. Potential solutions can run the gamut from getting evermore creative with procedures to address engineering deficiencies, to investing in new equipment, to building new facilities. Each approach has its pros and cons and therefore, the decision on which direction to take is complicated. The decision should consider factors such as process robustness, cost, regulatory hurdles and ongoing compliance. These factors inherently create a dynamic tension between maintaining the status quo vs. improvement and innovation. Many of us have older facilities, running older (well-established) processes, and we find ourselves compensating with creative solutions rather than taking the leap and adopting new technology or innovating. So why is this? Shouldn't innovation be encouraged and supported? Some of the uncertainty seems to be related to the perceived lack of clarity regarding expectations from regulatory authorities. Credit should be given, however, as regulatory authorities seem to be making progress as supported by the recent decision that water for injection made via distillation or reverse osmosis is now considered acceptable by both U.S. and EU regulators.

NEXT STEPS

If after considering the questions above you feel you do have an aging facility and are perhaps suffering from a bit of paralysis by analysis, consider reaching out to us for a conversation. We can help you develop a plan to include both immediate (e.g. document rationale and risk assessment for atypical layouts) and long-term (e.g. strategic plan and discussion with regulators) fixes.

Contact pharmamail@nsf.org or USpharma@nsf.org in the U.S.

Revision of ISO 14971, Risk Management for Medical Devices



by Oliver Christ,
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ISO 14971:2012, Application of Risk Management to Medical Devices – a harmonized standard in Europe under the Medical Devices Directives – has been under revision since October 2016. This important standard has been referenced by more than 250 safety standards for medical electrical equipment and systems, in-vitro diagnostics (IVDs), implants, software and usability.

This third revision of the standard is being conducted by joint working group JWG1. The parent committees IEC TC62A and ISO TC210 authorized JWG1 to conduct the revision based on a detailed analysis of which areas the standard needs improvements. Triggered by the overhaul of the European Medical Devices Regulations (MDR, IVDR), four major areas have been identified:

- > Clinical benefits and risk-benefit analysis (benefit-risk ratio, risk-benefit determination, etc.)
- > Production and post-production information related to risk management
- > Data privacy and security aspects (may need to be transferred to a separate standard)
- > Clarification of the relationship with IEC 62366-1, Application of Usability Engineering to Medical Devices

Major deviations from the existing risk management concept are not expected; rather, incremental improvements to help guarantee sustainability. In 2017, three international meetings of JWG1 took place in Tel Aviv, Israel (Feb. 2017); Delft, the Netherlands (June 2017) as well as Hiroshima, Japan (Oct. 2017). The first committee draft (CD) of ISO 14971 (third edition) was circulated in late 2017 for comment to all Member States working under ISO and IEC for medical device standardization. Comments on the CD1 shall be submitted until March 2018. The next international meeting is scheduled for early April 2018 in London where comments will be discussed.



JWG1 is working on three parallel documents: ISO/IEC Guide 63, Guide to the Development and Inclusion of Safety Aspects in International Standards for Medical Devices, the revision of ISO 14971:2007 and the revision of ISO 24971:2013, Guidance on the Application of ISO 14971.

With the work on ISO/IEC Guide 63, key nomenclature (e.g. harm, stakeholder and state of the art) will be revised, and sections currently organized as informative annexes of ISO 14971 will be restructured and transferred to the guidance document ISO 24971.

The standardization process for the third edition is expected by the end of 2019 to have a revised version of ISO 14971 available for conformity assessment under the new MDR by 2020. For further questions regarding risk management for medical devices, please contact Oliver at oliver.christ@prosystem-ag.com.

Oliver P. Christ, Dipl.-Ing. has been a member of JWG1 since 1996 when the committee was established. He comes to NSF International with the recent acquisition of PROSYSTEM AG.



by Jesse Ahrendt,
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Tech Talk



What Does Poor Quality Cost?

The cost of quality. A simple statement and yet few companies in the pharmaceutical manufacturing industry are paying close enough attention to this concept. Corporate focus, and rightly so at times, is for the most part focused on compliance and meeting regulatory requirements to sell products across the globe. Those compliance regulations require companies to perform at a prescribed level and maintain certain required systems.

Some of those quality systems include familiar functions such as incoming inspections, preventative maintenance and calibrations, complaints and returns, recalls, inspection and CAPA teams, environmental monitoring, rework and reprocessing. These are supportive systems that every company must have to maintain its overall compliance with industry expectations, but they come with their own internal costs. These are generally highly visible, obvious items and are easily shown on financial statements, often with a simple calculation of the total number of employees, their time allocated to these tasks and their respective fully-loaded salaries for each system or group. There are however a significant amount of hidden and less obvious costs that come along with those systems. These costs can be very large, depending directly on the level of quality in each respective area. When these costs are high, they are directly tied to the concept of poor quality.

The Reality of the Cost of Poor Quality

Poor quality costs have many hidden sources. For instance, in a recent situation, a client was experiencing a very large number of non-conformance investigations on the order of 2,000 to 3,000 per month. An investigation into this issue identified numerous underlying issues with the deviation processing systems, including inconsistent coding for non-conformances, superficial investigations that lacked root cause analysis, lack of effectiveness checks, lack of any formal training for investigators and simply an overwhelmed quality group. The costs associated with repeat deviations, rejected product, human investigation time, excessive planning to accommodate the workloads and employee turnover were massive.

But how are these costs identified/calculated and what impact can they have? When discussing a methodology like the cost of

quality it is sometimes easier to consider the rising costs of allowing a single defect to be processed through a manufacturing system. It is understood in the manufacturing industry by most quality experts that the cost of a defect will increase ten times at every major processing point if it is not caught. Simply stated, if a product defect is not prevented, perhaps during an incoming inspection or a routine monitoring process, it will cost ten times more to address the problem during production via rework, reprocessing and/or investigation time. If the defect was not caught internally and the impacted product was distributed, the cost to remedy the defect via return, recall and investigation would be another ten times, resulting in a 100-fold cost increase versus having prevented the problem initially.

This illustrates that if a company can spend \$10,000 to prevent a defect, it could avert spending \$100,000 to correct the problem internally and \$1,000,000 to address the problem once the product has been distributed. This scenario illustrates the larger ROI potential that exists when companies focus their efforts and resources on prevention of defects in their processes.

NSF Recommendations

Given these benefits, how does NSF recommend companies begin to identify and tackle the cost of poor quality (COPQ) opportunity that exists within their organizations? First we recommend that companies identify what their baseline COPQ is, which will require an evaluation of existing processes and their associated costs. This exercise will also help the effort to get further traction from senior management once they realize the substantial hidden costs attributed to poor quality. NSF's approach is to group quality costs into four main categories: prevention, internal failures, external failures and appraisal costs. These four groups and our methodology are detailed in the **Cost of Quality: Can We Really Afford to Ignore It?** white paper written by NSF's Andy Barnett – visit www.nsf.org/info/pblibrary.

Once the baseline has been established, a strategic plan must be developed to explore the opportunities for improvement that became readily visible via the COPQ baseline. Opportunities to eliminate defects are prioritized and poor quality is eliminated from the processes, which is the intended outcome. The ROI on projects our experts at NSF have undertaken have been staggering, typically ranging from 10 to 60 times!



NSF is passionate about the COPQ and is here to partner with and assist clients in their ultimate success, both in the role of compliance experts (which we are perhaps better known as) and in facilitating a targeted reduction in poor quality within their organizations. Targeting and eliminating hidden quality costs at all points along the manufacturing process should be a priority for any successful pharmaceutical/biotechnology company. We look forward to any inquiries and questions your organization may have on how to conduct and measure your own cost of poor quality initiative.

Contact us at USpharma@nsf.org.



by Pete Gough,
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& Andrew Papas,
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Regulatory Update



EU News

New GMP Legislation

In late September 2017 the European Commission published new GMP legislation in the Official Journal of the EU. Directive 2017/1572 covers GMP for marketed products and delegated Regulation 2017/1569 covers GMP and inspections for investigational medicinal products. As a consequence, the current EU GMP Directive 2003/94/EC will be repealed.

This new GMP legislation will become effective at the same time as the CT Regulation 536/2014 is implemented and the current GMP Directive 2003/94 will be repealed on the same date.

Clinical Trials

The minutes of the European Medicines Agency (EMA) management board meeting that was held on October 5 revealed that the CT Regulation 536/2014 is now not expected to be implemented until the second half of 2019 after the UK has left the EU.

The EMA has published a revised *Guideline on strategies to identify and mitigate risks for first-in-human (FIH) and early clinical trials with investigational medicinal products*. This guideline, which updates the 2007 version, was adopted on July 20, 2017 and becomes effective on February 1, 2018. This revised guideline addresses the lessons learned from the Phase I trial of Bial-Portela & Ca.S.A.'s FAAH inhibitor in France last year, in which one healthy volunteer died.

EU GMP Annex 1, Sterile Products

In late October 2017 Andrew Hopkins of the UK MHRA, who is leading the rewrite of this annex, said that a final text had been agreed and approved by the European Commission so the draft was expected to be published shortly. However, at the time of going to press in late November it had still not been issued.

EU GMP Annex 17, Real-Time Release

The final version of this revised annex is reported to have been approved by the Commission and is also expected to be published shortly.

EU GMP Annex 21, Medicinal Product Importation

In October 2017 it was reported that the drafting of Annex 21 was nearing completion, but fiscal importation was a sticking point due to different definitions between parties across the EU. It is hoped that a draft might be published in early 2018.

EU-U.S. Mutual Recognition Agreements (MRAs)

On October 31 the U.S. FDA announced that it had determined that it could recognize eight European drug regulatory authorities as capable of conducting inspections of manufacturing facilities that meet FDA requirements: Austria, Croatia, France, Italy, Malta, Spain, Sweden and the United Kingdom. This means that the EU-U.S. MRAs started, for these eight countries, on November 1 as planned.

ICH News

Membership

At the International Council for Harmonisation (ICH) meeting in Geneva in November 2017, the Singapore HSA regulatory authority was admitted as a member. The Colombian regulator INVIMA and the Bill and Melinda Gates Foundation were admitted as observers. Following this meeting, the ICH now has 15 members and 24 observers.

Q11 Q&A

The final, Step 4 version of the question-and-answer document *Selection and Justification of Starting Materials for the Manufacture of Drug Substances* was published in August 2017.

This document provides additional clarification and promotes convergence on the considerations for selecting and justifying starting materials and on the information that should be provided in marketing authorization applications and/or master files. The document focuses on chemical entity drug substances.

According to the document, the general understanding is that APIs that have already been accepted by regulatory authorities (e.g. for use in authorized medicinal products) do not have to be re-justified against the ICH Q11 general principles or the recommendations included in the Q&A document, unless significant changes are made to the API's manufacturing processes and controls. However, a starting material accepted for one manufacturer's process may not be considered acceptable for a different manufacturer's process if it does not comply with the guidance in ICH Q11.

A decision tree is provided in Annex 1 to serve as a pictorial exemplification to apply all ICH Q11 general principles for the selection and justification of a starting material.

Q12

The Expert Working Group approved the final draft of Q12 at the ICH meeting in June 2017. However, it did not receive Step 2 approval as, unusually, the EU required a legal check (the U.S. always does this but it is unusual for the EU) to

ensure that concepts in Q12 such as established conditions are compatible with EU law.

A revised version of Q12 did reach Step 2 in November 2017 and will be published with a longer than usual public commenting period. The European Commission insisted that wording be added to the effect that the draft Q12 guideline is not fully compatible with the established EU legal framework with regard to the use of established conditions referred to in Chapter 3 and with the product lifecycle management referred to in Chapter 5. So these provisions would not currently be able to be implemented in the EU.

Brexit News

Amsterdam Is New EMA Host City

The new host city for the EMA is Amsterdam in the Netherlands. The voting to select the new host was very close and Amsterdam beat Milan, Italy by the drawing of lots when the votes for the two cities were tied. This choice has been well received by industry and by the EMA itself. The EMA's executive director Guido Rasi remarked that it "ticks many of our boxes" and said that a joint governance structure would be set up to oversee the relocation project. Amsterdam was one of the cities that an internal EMA poll indicated had the best chance of retaining a significant proportion of existing staff and hence minimizing the disruption to their work as result of the move.

The EMA has set up an Operation and Relocation Preparedness Task Force, which has four work streams:

- > Relocation preparedness
- > Operational and financial preparedness
- > HR related matters
- > Communication actions

EMA has also established Working Groups on its numerous committees' operational preparedness for human and veterinary medicines, which will explore options for a reasonable and robust allocation of the workload currently done by the UK MHRA related to both human and veterinary medicines across the network.

Regulatory Update

UK Position

As far as medicines are concerned, the UK government position appears to be that it would like processes to continue as if it were still in the EU post-Brexit. It remains to be seen if this desire is shared by the remaining 27 EU Member States. The UK will become a third country after the end of March 2019 so unless the UK can agree a medicinal products sector-specific trade deal or transitional arrangements, there is the potential for seismic changes to the processes of placing medicines on the UK and EU markets.

In its online publication MHRA and making a success of Brexit, the UK MHRA states it would like to continue "to play a full, active role in European regulatory procedures for medicines" post-Brexit.

The UK Parliament's Commons Select Health Committee has launched an inquiry into the regulatory arrangements needed to guarantee safe and effective supply of medicines, medical devices and products post-Brexit. The Health Committee considered inputs on the following questions:

- > What are the key considerations that arise for companies, health care services and regulatory bodies in the UK as a result of the UK's withdrawal from the EU?
- > Following the UK's withdrawal from the EU, what alternative arrangements for the regulation of medicines, medical devices, medical products and substances of human origin could be introduced?
- > How much time is needed to facilitate a smooth transition to new arrangements? Is it possible, or desirable, to move directly to new arrangements post 29 March 2019, or are transitional arrangements needed?
- > How will withdrawal from the EU affect the UK's ability to influence international standards in life sciences?
- > What arrangements are needed to ensure the safe, effective and timely supply of medical radioisotopes over the short, medium and long-term?
- > What are the implications for medical research and development, including for the timely patient access to new medicines, technologies and other relevant medical innovations developed within or outside the UK?

PIC/S News

Following the Pharmaceutical Inspection Cooperation Scheme (PIC/S) Committee meeting in Taiwan on September 11-12, Mexico's Federal Committee for Protection from Sanitary Risks (COFEPRIS), the Turkish Medicines and Medical Devices Agency and Iran's Food and Drug Administration have been accepted as PIC/S members and will officially join the scheme on the January 1, 2018.

The Saudi Food and Drug Authority and the Russian ministries responsible for domestic and foreign GMP inspections have applied for PIC/S pre-accession, the first part of a two-stage application procedure for membership. Along with Kazakhstan, this makes three countries in the PIC/S pre-accession stage, which serves to identify any gaps between PIC/S membership requirements and the system used by the applicant's competent authority. The maximum timeframe for the pre-accession process is two years upon receipt of a completed audit checklist and questionnaire.

The Philippines Food and Drug Administration applied for PIC/S membership in 2009 but is undergoing a reorganization and has also applied to be listed as an Association of Southeast Asian Nations (ASEAN) competent authority. PIC/S has invited it to reapply for PIC/S membership once it has completed the ASEAN assessment process.

U.S. News

New Principal Deputy Commissioner

In August 2017 FDA Commissioner Scott Gottlieb announced the appointment of Rachel Sherman as Principal Deputy Commissioner, the second highest position in the FDA. This is not a new position but this role has not been filled permanently since Josh Sharfstein left in 2011.



Sherman will oversee all medical programs and initiatives that are agency cross-cutting and clinical, scientific and/or regulatory in nature. Sherman also will “provide advice and counsel relating to medical product regulation” and work with the Commissioner to “develop and implement several key agency initiatives,” according to a memo from Gottlieb to FDA staff.

Concept of Operations

The FDA has produced the document *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations*. It is dated June 6, 2017 but was only given prominence in August 2017 by the enactment of user-fee renewal legislation (FDARA) that included mechanisms for speeding drug approvals.

This concept of operations white paper discusses how the Center for Drug Evaluation and Research and the Office of Regulatory Affairs will work in a vertically-integrated, programmatically-aligned environment regarding application review and inspections, and the associated compliance activities.

The concept of operations agreement will help FDA meet a new commitment to tell drug firms, branded and generic, how the agency has classified their facilities within 90 days of inspection.

The document provides an operating model, a flow diagram and a RACI chart, in Attachments 2 and 3, for each of the following:

- > Pre-approval facility evaluations and inspections
- > Post-approval facility inspections
- > Surveillance facility inspections
- > For-cause facility inspections

The new concept of operations complements the Program Alignment Group initiative’s reorganization of FDA’s Office of Regulatory Affairs.

FDA Draft Guidance on Identifying Trading Partners Under the DSCSA

In late August 2017 the FDA issued further draft guidance to clarify the roles of the different supply chain partners under the Drug

Supply Chain Security Act (DSCSA). This law mandates that pharmaceutical manufacturers only accept drug products from and transfer drug products to authorized trading partners, or parties that are properly licensed or registered to receive or transfer products. The DSCSA identifies five types of entities in the prescription drug supply chain: manufacturers, re-packagers, dispensers, wholesale distributors and third-party distributors.

The draft clarifies that under the DSCSA the position in the U.S. will be the same as in the EU; i.e. if a manufacturer is only distributing its own drug, it would not be engaged in wholesale distribution under DSCSA, and would not be required to comply with the licensure and reporting requirements for wholesale distributors under DSCSA (in the EU a manufacturing site holding a manufacturing authorization does not need a wholesale authorization to distribute products made at that site).

FOR THE LATEST INDUSTRY REGULATIONS AND NEWS AS THEY HAPPEN, DOWNLOAD OUR PHARMA APP

A NEW ERA OF DATA PROTECTION

You, Your Customer and GDPR



by Heather Taylor, Director of Marketing, NSF Health Sciences

In April, 2016, after four years of discussion, the new EU data protection framework was adopted. It takes the form of Regulation (EU) 2016/679 – the **General Data Protection Regulation (GDPR)**. On May 25, 2018, the GDPR will replace the current Data Protection Directive 95/46/EC and will be directly applicable in all Member States without the need for implementing national legislation.

As companies begin the process of moving to compliance with the new requirements, Member States are carefully considering the impact on national data protection legislation. In reality, national laws will need to be amended in order to regulate aspects such as transitional rules or implementation of additional requirements where discretion is given by the GDPR. The first draft national laws with necessary legislative changes have already been published in Germany, the Netherlands and Poland.



The new regulation is quite comprehensive and will take time to prepare for. The following tips will help you get started:

- 1. Prepare for data security breaches.** Put in place clear policies and well-practiced procedures to ensure that you can react quickly to any data breach and notify stakeholders where required.
- 2. Establish a framework for accountability.** Make sure that you have clear policies in place to prove that you meet the required standards.
- 3. Embrace privacy by design.** Ensure that privacy is embedded into any new processing or product that is deployed.
- 4. Analyze the legal basis on which you use personal data.** Consider what data processing you undertake. Do you rely on data subject consent for example, or can you show that you have a legitimate interest in processing data that is not overridden by the interests of the data subject?
- 5. Check your privacy notices and policies.** Your policies should be transparent, easy to understand and easily accessible.
- 6. Bear in mind the rights of data subjects.** Be prepared for data subjects to exercise their rights under the GDPR, such as the right to data portability and the right to erasure.
- 7. If you are a supplier to others, consider whether you have new obligations as a processor.** The GDPR imposes some direct obligations on processors which you will need to understand and build into your policies, procedures and contracts.
- 8. Be careful with cross-border data transfers.** Ensure that you have a legitimate basis for transferring personal data to jurisdictions that are not recognized as having adequate data protection regulation.

Looking for further reading? View the EU GDPR website – www.eugdpr.org, the Union's official website for the regulation detailing all you need to know, or if you have more time, view the full regulation itself.



Staff Updates



TOM DZIEROZYNSKI PROMOTED TO EXECUTIVE VICE PRESIDENT OF NSF INTERNATIONAL'S GLOBAL PHARMA BIOTECH BUSINESS

Tom Dzierozynski, formerly the Executive Vice President of NSF Averant, has taken on responsibility for NSF International's global pharma biotech business.

Tom joined NSF with the August 2015 acquisition of Avarent LLC, a medical device consulting firm. He has over 20 years' experience in the pharmaceutical, medical device and biologics industries. Through comprehensive and practical knowledge of operations, regulatory affairs and quality systems, he has developed and implemented risk-based strategies that integrate varying business functions to drive ownership and improve operational and quality performance.

Tom has led technically-oriented projects focusing on design controls, verification and validation, process improvement, regulatory market clearance, risk management and implementation of corrective actions to address/avert enforcement actions. Earlier in his career, Tom was Vice President of Validation Services for Quintiles Consulting, and held quality, engineering and management positions at Baxter Healthcare Corporation.



NSF WELCOMES NEW DIRECTOR CATHERINE KAY TO THE TEAM

Catherine Kay joins NSF International as a Director of Pharma Biotech in Europe. Catherine has extensive pharmaceutical operations management, technical and QA experience spanning more than 22 years, working for a major international pharmaceutical organization, a start-up manufacturing organization and, most recently, a contract manufacturing organization in a corporate operations role.

She has experience in being responsible for the operational start-up of a new solid dose manufacturing and packaging facility, from design and set-up of systems, procedures and processes to the supply of medicinal products to the global market, meeting EU and FDA GMP regulations and requirements.

Catherine is passionate about developing people and creating learning organizations, with continuous improvement embedded into daily operations and will therefore be taking a focus on NSF training. She has a keen interest to support the Qualified Person courses, as well as developing an e-learning program in the very near future.

NSF and IDMA Launched Advanced Program in Pharmaceutical Quality Management

On September 25, 2017, NSF's Global Vice President of Pharma Biotech and Medical Devices, Martin Lush, went to India to join the team and launch NSF's advanced program in pharmaceutical quality management (APPQM), in collaboration with the Indian Drug Manufacturers' Association (IDMA).

Martin Lush, who is spearheading this program, spoke at the event along with S.M. Mudda, Project Director of APPQM and Director-Technical of Micro Labs Ltd. in Mumbai. They emphasized that the industry needs to keep the patient at the center of business and balance profits, efficiency, legacy and reputation with customer service.

Over 40 pharma professionals from many backgrounds attended the event and have completed the first two modules. The aim of the program is to increase the number of globally certified pharmaceutical quality professionals based in India, therefore providing an ideal opportunity for companies who want to grow their business in Europe and the U.S. The program also addresses a shortage in skilled staff required by GMP-approved pharmaceutical manufacturers in India.

If you are interested in joining the program and want more information, view the APPQM brochure or get in touch at pharmamail@nsf.org.



NSF Exhibits at Pharma Integrates 2017



On November 15 and 16, NSF's Martin Lush and John Johnson exhibited at Pharma Integrates 2017 in London. Martin facilitated two panel discussions on how to improve efficiency and effectiveness of pharma R&D; Rethinking Pharma Productivity and De-Risking Pharma. The first session focused on changing the way pharma thinks about production, processes and people, while the second session looked at how pharma views, manages and assesses risk. Visit NSF's pharma LinkedIn profile to watch the full recording of the session on risk.



PQG's 40th Anniversary Event NSF Continues Support

NSF's pharma biotech team was happy to support the Pharmaceutical Quality Group's (PQG's) 40th anniversary meeting in Milton Keynes, UK on October, 9-11, 2017. Pete Gough, NSF's Executive Director of Pharma Biotech, presented regulatory and legislative update sessions on both the trainee QP day and at the main meeting that followed on Tuesday and Wednesday. John Johnson, NSF's Vice President of Pharma Biotech, presented a session on best practice behaviors for perpetual GMP compliance, while David Waddington, NSF's Director of Pharma Biotech, presented a serialization update session. David Begg, the founder of DBA (which was acquired by NSF International in 2007), gave a speech at the celebration dinner on Monday evening.

It was good to meet new and existing clients at the event that covered topical issues facing the pharma industry today and we look forward to continuing our support of the PQG in coming years.



If you would like a copy of the NSF presentations, please contact pharmamail@nsf.org.

TRAINING COURSE ATTENDEES WIN RECOGNITION

Recently, two attendees of our pharmaceutical training courses received recognition.

Clare Myatt Receives NSF's 2017 QP Alumni Award for Outstanding Academic Achievement

We are delighted to announce Clare Myatt has received NSF International's 2017 QP Alumni Award for Outstanding Academic Achievement. In recognition of the hard work and dedication Clare continually produced throughout her QP training and MSc study program, the team at NSF would like to say well done. Clare is a member of NSF's QP alumni group, which is focused on providing invaluable continuing professional development (CPD) for the busy QP and lifelong support after the course is completed.



Clare Myatt

"I was honored and truly surprised at receiving the QP Alumni Award for Outstanding Academic Achievement 2017 in recognition of the work I had produced throughout the Qualified Person training and MSc study program. I have genuinely enjoyed the entire QP journey and with the support, education and resources received from the team at NSF and the University of Strathclyde – as well as my fellow delegates – meant I had every chance of success."



From left to right – Graham Kench, Member Manager at CQI and IRCA, Sandra O'Reilly, Mike Halliday.

1,000th Delegate on Pharmaceutical GMP Audits and Self-Inspections Course

NSF would like to congratulate Sandra O'Reilly from Dr. Reddy's Laboratories (UK) who was the 1,000th delegate on NSF International's CQI and

IRCA Certified GMP PQS Lead Auditor training course.

Mike Halliday, NSF International's Executive Vice President of Pharma Biotech, said *"it was a pleasure to work with Sandra on the course and we are delighted to also say Sandra passed the course assessment."*

For more information on these courses, visit www.nsf.org/info/pharma-training.

Forthcoming Courses & Events

What's Planned for February to April 2018

GMP for Biological and Biotechnology Products

February 27 – March 2

Manchester, UK

Course Fee: £2,370 excl. VAT

Pharmaceutical Quality Systems

March 12 – 16

York, UK

Course Fee: £3,395 excl. VAT

Free QP Seminar for Prospective QPs and Sponsors

March 13

York, UK

Course Fee: FREE

Pharmaceutical GMP

March 19 – 22

Amsterdam, Netherlands

Course Fee: £2,370 excl. VAT

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

March 20

Manchester, UK

Course Fee: £790 excl. VAT

WORKSHOP | Regulatory Affairs for QA: Marketing Authorizations

March 21

Manchester, UK

Course Fee: £695 excl. VAT

WORKSHOP | Regulatory Affairs for QA: Variations

March 22

Manchester, UK

Course Fee: £695 excl. VAT

A-Z of Sterile Products Manufacture

April 16 – 20

Manchester, UK

Course Fee: £3,090 excl. VAT



Pharmaceutical GMP Audits and Self-Inspections

(A CQI and IRCA Certified Training GMP PQS Lead Auditor Course)

April 16 – 20

Manchester, UK

Course Fee: £2,970 excl. VAT

Pharmaceutical Microbiology

April 23 – 27

York, UK

Course Fee: £3,395 excl. VAT



Quality Risk Management

April 24 – 25

Stansted, UK

Course Fee: £1,580 excl. VAT

RELATED COURSE Quality Risk Management for Sterile Products

18 – 20 June

York, UK

Course Fee: £2,060 excl. VAT

Events We Will Be Exhibiting and Speaking At

Making Pharmaceuticals Europe

March 13 – 14

Brussels, Belgium

Making Pharmaceuticals UK

April 24 – 25

Coventry, UK

Early bird or multiple delegate discounts apply to some of our courses. Please contact us for full details on all our available discounts.

For more information, email pharmacourses@nsf.org or visit 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.

2018 Webinar Program



January 17:

NSF's New Workshops on Regulatory Affairs for QPs and QA

February 23:

Shaping the Role of the QP, Now and for the Future

February 27:

How to Prepare for Excipient GMP Certification

March 7:

Performing Quality Risk Assessments on Sterile Products and an Update on Annex 1

April 4:

A Proactive Approach to Quality Risk Management

April 11:

The Changing Face of the EU and the Implications of Brexit to the Pharma Industry

April 25:

Pharmaceutical Quality Systems

May 2:

New Approaches to Validation: Trends and Best Practice

May 9:

Using Behavioral GMP to Create Perpetual GMP Inspection Readiness

May 22:

Regulatory Perspectives on Data Integrity

June 12:

Introduction to ISPE's Cultural Excellence Report and How It Changes Our Current Thinking

June 27:

A Structured Approach to Improving Investigation Report Writing

July 10:

Managing Critical GMP Incidents and How to Reduce the Consequences and Risk of Recurrence

July 11:

Applying the CAPA Hierarchy to Identify Highly Effective Corrective and Preventative Actions

September 18:

Good Clinical Practice and Pharmacovigilance for QPs and QA

September 19:

How to Manage International Supply Chains Through Effective Outsourcing

October 30:

Sharpening the Saw: How to Use Audits As a Way to Prevent Issues Becoming a Crisis

November 13:

Managing a Quality Network, Real or Virtual

You can register online and read further about the webinar content on our website www.nsf.org/info/pharma-webinars

NSF'S E-LEARNING COMING YOUR WAY APRIL 2018



For more information contact us at e-pharma@nsf.org

You can already access a full range of free e-learning resources at www.nsf.org/info/pblibrary

Review of Quality System SOPs

by Andy Barnett

CLIENT:

Large international pharmaceutical manufacturer.

SITUATION:

NSF's client requested a proactive review of major quality systems and procedures in response to a warning letter.

SOLUTION:

NSF reviewed and critiqued essential quality systems SOPs against regulatory standards and industry best practices. This included sampling plans, CAPAs, risk assessment, calibration, preventive maintenance, etc. We verified that actual practice complied with SOP commitments and remediated as necessary.

FINDINGS:

Risk Assessment SOP

We discovered this particular SOP had an error in the risk scoring definitions for detectability. The "as found" definitions and risk scoring grid were:

Severity x Frequency	9	9	18	27
	8	8	16	24
	7	7	14	21
	6	6	12	18
	5	5	10	15
	4	4	8	12
	3	3	6	9
	2	2	4	6
	1	1	2	3
		1	2	3
		Detectability		



DETECTABILITY:

VALUE	P: Probability
1	High: No mechanism for detection
2	Medium: May be detected at a later stage
3	Low: Will be detected immediately

The definitions for detectability were reversed! High-risk items were given a low score and low-risk items were given a high score. 14 of the 27 scoring combinations were affected, resulting in incorrect evaluation of overall risk.

BENEFITS TO CLIENT:

The SOP was fixed. The company performed a retrospective review of management review/prioritization decisions, focusing on items that had low overall risk, but should have been high. Once the SOP was fixed, the company properly prioritized all risk-based events.



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