

# Journal

Issue 30, Fall 2014

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## How to Talk to Senior Leaders in a Way They **Can't Ignore**



Health Sciences  
Pharma  
Biotech

*Formerly NSF-DBA*

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# welcome

Welcome to the Fall edition of the Journal. We hope that you enjoyed a great Summer break. After a Summer shutdown and some valuable time with your families, I am sure that you are raring to get back into production. Across the industry, the final quarter of the calendar year can be a hectic time, so we have prepared an action-packed Journal that should help you get out of your shorts and sandals, and back to the swing of formulation, testing and supply of high quality pharma products.

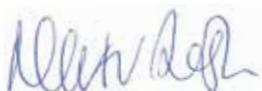
The theme for this issue is 'variety'. The Tech Talk article on **Planned Shutdowns** will help you successfully manage your next one with relative ease. Written with the help of my old plant engineer at AstraZeneca, Paul Merrick, we hope you can learn from our mistakes!

Whilst many companies are struggling to modernise or make efficiencies to their **Quality Management Systems**, John Johnson describes what is possible by sharing the secrets from the experts in the automobile industry.

Our main feature is an interview with one of my colleagues, Mr Frank Dollard. The idea for the feature came following a meeting with a client bemoaning the fact that 'management were not listening to his recommendations'. When he ran through his presentation it was clear why. He simply wasn't speaking their language and he used the 'compliance' word so many times even I became bored. In his 40+ years in our industry Frank worked his way up from the shop floor to the boardroom. His advice on **how to communicate with business leaders** is priceless and you ignore it at your peril.

You will also find Pete Gough's no-nonsense interpretation of the **latest rules and regulations**, written in a way only Pete can, together with a summary of our **key education courses all designed to make your life easier**.

On behalf of all of us at NSF Health Sciences, we hope you had a great Summer vacation with your family and friends. And of course don't forget, if we can help you make it a stellar fourth quarter for you and your company, we are right by your side.



Martin Lush



Martin Lush  
President,  
NSF Health Sciences  
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# Tech Talk



## Facility Shutdown Management: Best Industry Practices

### to Ensure a Smooth Shutdown and a Rapid Startup

Martin Lush underlines the importance of controlling plant shutdowns so that start-up is on time with minimal disruption to the ongoing supply of products.

“We all have our war stories of shutdowns dragging on for weeks, not days, and it is worrying that after many engineering interventions it can take weeks or even months before the facility performs as well as it did beforehand,” says Martin. “What can you do to make sure this important event is performed rapidly, under close control and within the cGMPs?”

### Facility Shutdown Maintenance: The Context

Facility or “planned” shutdown maintenance is vital for any production facility. Access to these plants and equipment is usually restricted during routine operations, so planned shutdowns provide the opportunity for the engineering team to complete major maintenance to the plant as well as equipment.

However shutdowns can come in many shapes and sizes!

- The genuinely planned! These are usually scheduled well in advance for large-scale maintenance activities. The number of these planned shutdowns depends on the nature of the manufacturing process and how hard the plant is working, the so-called plant utilization. The greater the plant utilization, the more (preventative) maintenance is required. When companies wrongly perceive these to be a cost, not an investment...they are in trouble. This is like

waiting for your car to break down rather than having it regularly serviced

- The unplanned emergency shutdown. A leaking pipe or a catastrophic equipment failure usually happens when you least expect it and usually at the worst time possible. To fix it, the plant must be shut down quickly in a controlled way
- Full and partial shutdowns. Planned shutdowns usually involve closing the entire plant. Emergency shutdowns sometimes require only partial closure, presenting some unique challenges for startup and maintaining high quality product supply

Shutdowns represent a high risk to your operation and are costly!

- Lots of contractors and third parties are usually involved. All must be managed
- The build up to shutdowns can be rushed as plants frantically attempt to “catch up” with stock build and manufacturing schedules



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



- It's amazing how some equipment never works as well as it did before it was stopped and had parts replaced! This can lead to delays, stress and frustration as plant engineers struggle to hit deadlines for startup. This burn in period can stretch for months and lead to further interventions and costly GMP incident investigations
- Change control! Changes to plant and equipment have to be reviewed within hours, not days or weeks; and the expertise has to be on hand to make this happen
- Long hours. It is not uncommon for engineering teams to work 24/7 to get the job done. Fatigue + Stress = Mistakes
- Since Job A must precede Job B, careful planning and scheduling is vital
- Too many cooks. Contractors, engineers, validation specialists, QA, QC, Procurement, Operations; all have a part to play. Without leadership, planning, control and short interval management, the outcome could be disastrous
- Contamination control. It is often the case that the job people least like doing is usually the most critical. In this case, post shutdown cleaning and sanitization can be a real chore yet they are critical in re-establishing environmental standards and control

No matter what type of shutdown (planned or emergency), the key to success is organization and discipline:

- Clearly defined roles and responsibilities
- Clear handover between each activity or shutdown phase
- Attention to detail, particularly cleaning and sanitization
- Exquisite control over plant access, contractors and CHANGES to plant, process and equipment

We hope the following checklist will help you!

## Shutdown Management: The Practice

No matter what type of shutdown it is, there are usually five key phases, each with key considerations. Think of it like a relay race:

**Phase One:** Pre-Shutdown Activities (Planning and Scheduling)

**Phase Two:** Declassification and Handover

**Phase Three:** Day-To-Day Management and Handover

**Phase Four:** Reclassification and Handover

**Phase Five:** Post-Shutdown Activities and Completion of the Shutdown Report

### Phase One: Pre-Shutdown Activities (Planning and Scheduling)

- Confirm who must do what. Accountability and specific responsibility for key shutdown roles:
  - ◆ Shutdown coordinators/planners
  - ◆ Shutdown leader
  - ◆ Plant owner
- Your shutdown management team. Who must be involved:
  - ◆ Engineering
  - ◆ Validation/technical operations
  - ◆ Manufacturing operations
  - ◆ QA
  - ◆ QC
  - ◆ Procurement
  - ◆ Safety
  - ◆ Planning or Sales and Operations team
- Generate a list of all shutdown activities to assess:

- ◆ Resources required (who, what, when)
- ◆ Timelines for each shutdown activity
- ◆ Lockdown dates to prevent any further additions to the schedule that can't be planned for
- ◆ Pay particular attention to any task that will directly impact all others, e.g. power supply outage and smoke pattern testing

#### Contractors and third parties:

- ◆ Competency screening and risk ranking. Are your contractors skilled and competent? Which will be responsible for conducting high-risk activities where the consequence of errors and mistakes could be costly?
- ◆ Contractual arrangements signed and sealed. What they can and can't do clearly defined and documented
- ◆ Control, communication supervision and management: Who will check their work once completed?
- ◆ Contingency planning. What if key contractors are unavailable? Do you have a plan B?
- ◆ Keep an eye out for subcontractors being engaged without the knowledge and consent of the shutdown owners! They can wreak havoc

#### Equipment replacement, consumables and spare parts (availability and lead time). Make sure you have plenty of the obvious available:

- ◆ Gowns/Tyvek suits
- ◆ Cleaning agents of all types
- ◆ Filters

#### Completion and publication of a Gantt chart showing key activities, resource requirements, roles and responsibilities for all key stakeholders and the exact support requirements:

- ◆ Contractors
- ◆ Manufacturing/operations

- ◆ Engineering
- ◆ Validation
- ◆ QA
- ◆ QC

#### Change control. Make sure that any planned changes to the plant and equipment are approved well in advance of the shutdown, not on the day

#### Criteria for handovers between each shutdown phase. Who will check and verify what, when and how? Making sure QA is involved in the approval process is key so that oversight can be maintained and the impact on products release assessed

#### It is vital to remind people that a plant in shutdown is still a GMP facility, not a building site. Make sure you have signage that gets this point across

### Phase Two: Declassification and Handover

#### Removal of everything that can be moved from the plant. All movable equipment and materials should be bagged, tagged and stored to prevent contamination

#### Equipment that can't be moved should be securely covered. Open pipes must be sealed/capped off to prevent contamination

#### Protection of walls and floors. During major shutdowns, walls and floors can be damaged requiring costly delays for additional repairs. If you expect a lot of heavy shutdown work, make sure you protect them

#### Sampling and monitoring points capped or sealed. If you have monitoring points, make sure these are sealed off

#### Audit (plant review) and sign-off vs. detailed checklist. Before you move to Phase Three, make sure you walk the plant to ensure that everything that should have been done has been done!

#### Words of Wisdom

*All you need is the plan, the road map, and the courage to press on to your destination.*

Earl Nightingale

**Phase Three:**  
Day-To-Day Management

- Controlled access. Shutdowns are not a free invitation for anyone to enter the plant. The more people wandering around, the greater the chance of losing control of the shutdown. Restrict access to those that matter
- Clothing requirements. Tyvek suits should be the minimum
- Contractor management:
  - ◆ Permit to work system (or equivalent) to ensure that contractor's tasks are agreed to beforehand and verified upon completion. A central location ("control room") for all work management is key. Visible, constantly manned...somewhere for people to go
  - ◆ Supervision. Make sure you have people providing day-to-day oversight and supervision of contractors based on the criticality (risk) of what they are doing
  - ◆ Verification upon completion
  - ◆ Remember, some contractors may not have a detailed understanding of the demands of working in a GMP environment. Make sure you provide an experienced local guide to oversee and to make sure they meet GMP requirements
- DAILY change control committees. Shutdowns can involve a lot of changes to equipment and the plant. Make sure these can be fast tracked for speedy approval with daily, face-to-face change control committee meetings for review and approval
- Requalification of equipment and plant. Any significant change to the plant and equipment usually requires requalification. Make sure it's done

- Waste removal. Major shutdowns can lead to considerable waste. Make sure this is removed immediately and is not allowed to build up
- Cleaning. During major shutdowns make sure cleaning accompanies every major activity to ensure contamination is controlled throughout, making the final clean-down easier
- Daily "snagging." Even the best planned shutdown rarely goes according to plan! After each day, complete a review of what is on track and what is not. What has gone according to plan...and what has not. This review of the snags or problems helps you in your contingency planning
- DAILY contingency planning with all key stakeholders. What extra resources are needed? How can additional risks be managed or contained?
- If you anticipate any delay to successful startup, inform your colleagues in planning ASAP! They hate surprises
- A DAILY "plan, do, review and adjust" must take place at the start of each day with all key stakeholders to ensure everyone knows what's going on

**Phase Four:**  
Reclassification and Handover

- Review and approval of requalification activities: Make sure that all equipment is operating within its validated state
- "Deep clean." This is one of the most vital activities of any shutdown and yet the one activity often poorly done. Sanitizing agents applied to dirty surfaces, hard to clean locations ignored, activities rushed, insufficient contact time...can all delay efficient startup due to poor environmental control. Here are the key phases:

- ◆ Firstly make sure your cleaning and sanitizing pattern or sequence does not contaminate already clean surfaces. Starting from the areas where product is open moving outwards; with the changing rooms and transfer hatches last on the list
- ◆ Pre-clean environmental monitoring. It's a good idea to take surface samples (swabs and contact plates) from a wide range of locations before any cleaning and sanitization activities. Pay attention to those notoriously difficult to clean locations
- ◆ Detergent wash. Most sanitization agents are only effective when applied to surfaces free from dirt. Cleaning all surfaces with a detergent is key
- ◆ Sanitization of all surfaces with a broad spectrum agent
- ◆ Sporocidal clean! Now it's time to hit the spores with an aggressive sporocidal agent
- ◆ Post-clean down environmental monitoring. Take surface samples from locations adjacent to those sampled before the clean down activities
- HVAC cleanup: Shutdowns and the cleaning and sanitization activities can generate a lot of contamination and the plant requires time to "clean up" in the resting state. Good HVAC systems will remove contamination and return the plant to its "at rest" state within 24 hours
- Confirmation that "at rest" conditions have been achieved for non-viable particulates
- Plant visual inspection. One last walk-through to make sure everything is shipshape
- Formal handover and sign-off. This is when the plant is formally handed back to operations

**Phase Five:**  
Post Shutdown Activities and  
Completion of the Shutdown Report

- Confirm environmental monitoring results. The question often asked is "Should we wait for a full set of microbiological environmental results before we can start to make product?" Recognizing the costly delay this could incur forces many companies to be pragmatic and allow manufacturing to start without microbiological data to prove the environment is in control, providing that:
  - ◆ Cleaning and sanitization have both been done effectively and signed off
  - ◆ Monitoring for non-viable particulates confirms that the facility has returned to its resting state
  - ◆ Everyone acknowledges that product manufactured during this period is done "at risk." In other words, if the micro environmental data is out of specification, product may be rejected
- Confirm plant and equipment are working within validated parameters
- Remember, some equipment may have been reset to the OEM-recommended baseline parameters. In reality, you often operate equipment to different parameters based on operational history, performance and validation studies
- Close out any remaining change controls
- Close out any deviation incidents
- Compile lessons learned. It's vital for everyone involved in the shutdown to do a lessons learned review before memories fade:
  - ◆ What went well?
  - ◆ What didn't?



◆ Improvements for next time?

Complete shutdown report. It's vital the report is completed quickly to include:

◆ Executive summary: A short paragraph of what went well, what didn't, any risks and how these have been managed or contained

◆ Completed handover checklists covering all activities

◆ Engineering status

◆ Validation status

◆ Change controls. Those closed, those open

◆ Deviations. Number, type, status

◆ Environmental control. Data to demonstrate the status of the plant for viable and non-viable particulates

Gain approval of the report by the shutdown leader (the author), QA and the plant owner

## Call to Action: What You Must Do For Your Next Shutdown – Top Five Action Points

- Customize the above and generate your own checklist for each of the key phases. Involve everyone in this process
- Make sure you have documented handover between each of the key phases. This involves the shutdown leader, the plant owner and QA reviewing completion of the key activities in the checklist
- Although good planning and coordination are key, shutdowns rarely go according to plan. Make sure your contingency plans are robust and your risk-based decision making skills are well practiced
- Remind everyone that the rules of GMP still apply: controlled access, contractor management, good documentation practices and so on
- Phase Five is key: Do the report immediately. Communicate the Executive Summary to QA (for the purpose of product release). Make sure you document lessons learned immediately while everything is fresh in your mind



# Case Study: Autoclave Problem – What Would You Do?

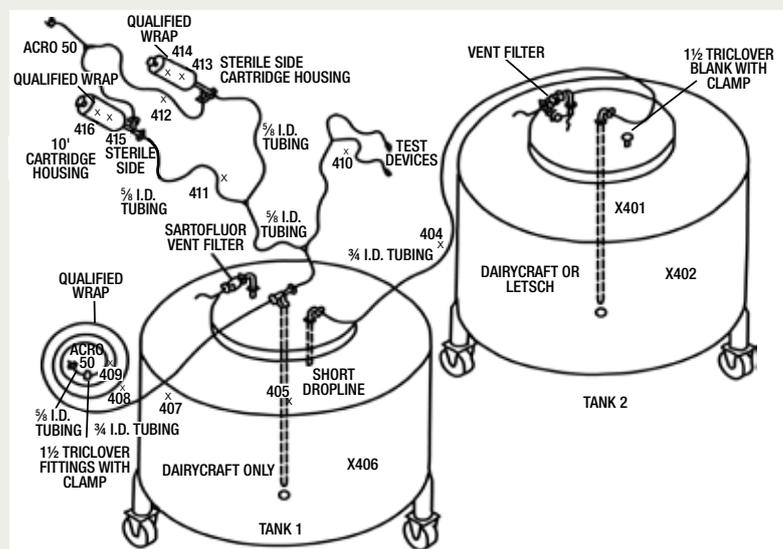
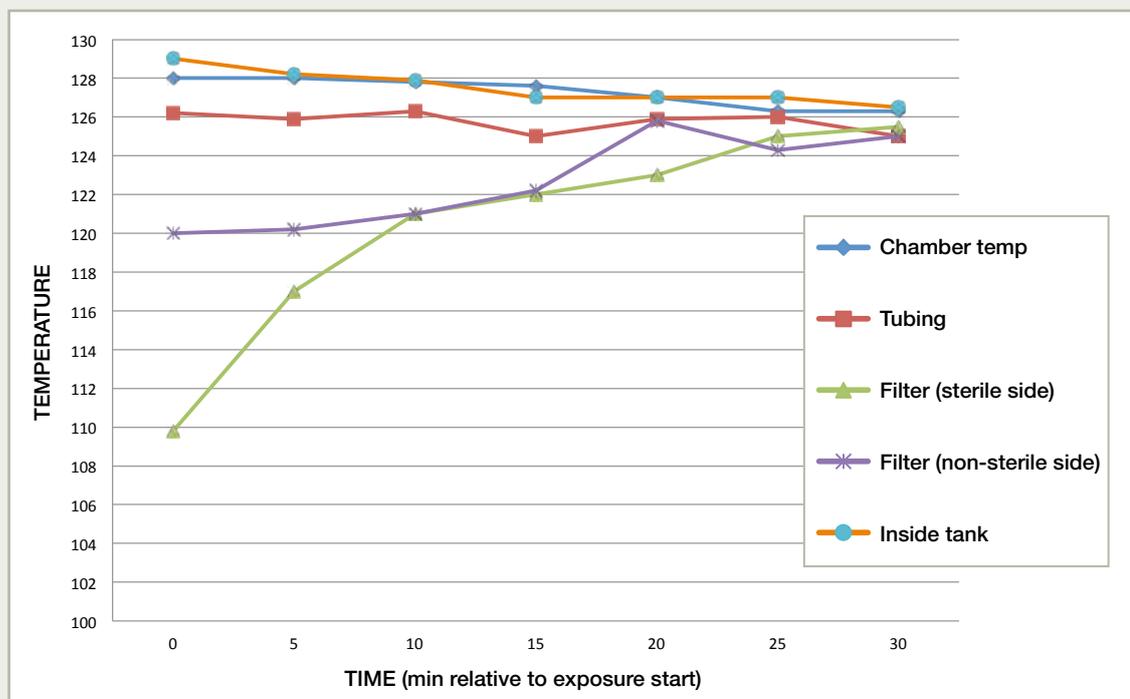
Moist heat sterilization (autoclaving) is vital to your process. It's complex and very high risk when things go wrong. It is absolutely vital you have expert knowledge of the principles and practice and what to do when things go wrong.

For those of you involved in moist heat sterilization, consider the following case study. Are there any concerns with this data? If so what could be done to overcome them?

The autoclave chart shows the temperature recorded at various points in the assembly, both shown below:

- Chamber temperature – free space
- Tubing – location 404
- Filter (sterile side) – location 413
- Filter (non-sterile side) – location 414
- Inside tank – location 402

Exposure started when all probes reached 100°C and therefore there was accumulation of F<sub>0</sub>. All probes show a minimum F<sub>0</sub> of 30 and all are above 121°C for at least 15 minutes.



- Discuss this case study with your colleagues. The more you practice problem solving, the easier it becomes
- List the contributing factors causing the poor performance
- What corrective and preventive actions would you take to minimize risk?

Turn to page 19 for the model answer.



# How to Get Your Message Across and Make Things Happen



Words of Wisdom

“Good business leaders create a vision, articulate the vision, passionately own the vision, and relentlessly drive it to completion.”

Jack Welch



by Martin Lush, President, NSF Health Sciences Pharma Biotech

## An Interview with Frank Dollard, Consultant, NSF Health Sciences

*During an anxious meeting with a client the other week, the head of Quality Operations was bemoaning the fact that “management wasn’t listening.” He was desperate for additional headcount so he could do more internal audits. Fair enough, I thought. After he presented his business case to me, it was clear why his plea had fallen on deaf ears.*

*His compliance case was strong, but his business case very weak. This highlighted a very common problem faced by ‘technical’ people – how to communicate with business colleagues and not get ignored. Fortunately, this is something one of my colleagues is very passionate about. During his 40 years in the pharma industry (research-based companies as well as generics), Frank Dollard worked his way up from raw graduate on the shop floor to the boardroom. From manufacturing multiple dosage forms to working with financial institutions on acquisitions and divestments...and everything in between.*

The question I asked Frank was *“How should those with a technical, operational and QA background communicate with business leaders to get things done?”*

Here were his top seven recommendations:

- Get into the real world
- Understand your business and your ‘Profit & Loss’
- Ban the term ‘Zero Risk’
- Establish a strong network of contacts
- Move away from reactionary firefighting to more strategic, value adding thinking
- Focus on preparation not presentation
- Publicize your success and build your credibility

*Frank:* Before I get into specifics one important caveat. My views, answers and recommendations will appear to be generalizations. Some are better at this type of communication than others but overall there’s lots of room for improvement. Most QA and technical ‘middle-ranking’ people are surrounded by people in similar positions and assume that key decision makers think the same way and talk the same language. They don’t. There is an old saying that “Communication is measured by the response you get.” If you’re not getting the right response, take a different approach. Here are my recommendations!

### Embrace the real world

The purpose of any free-market enterprise is to provide returns for investors. The

enterprise makes those returns by providing goods or services that it can create for a cost less than that for which it can sell. The greater the differential between these two values, the more successful the enterprise. It is clear that world-class companies pay meticulous attention to four activities which support this:

- Innovating new products or services
- Growing sales value/volume
- Reducing the time taken to provide the goods or service
- Minimizing unnecessary cost

The commercial and regulatory environment will remain brutal and only those that excel at the above will survive. Everyone must play their part. No one is exempt. The quality management system must be seen as a business management system owned by all with just one purpose – to improve your business’s competitive edge by:

- Reducing time to market
- Reducing manufacturing cycle time
- Reducing back-order value
- Reducing inventory (often used to hide many quality problems)
- Reducing product cost
- Increasing individual and team performance

Unfortunately, bureaucratic and overly

complex quality management systems do the complete opposite which is why Quality Assurance is seen as a cost sink in many organizations rather than an important part of profit generation.

*Martin: What would you say to companies who view the role of QA and the QMS as compliance enforcement?*

*Frank:* Get in the real world, change hearts and minds quickly because if you don’t, you won’t survive. Compliance in some cases is a minimal position, often imposed by external regulators, rather than a proper, risk-based assessment of your operation by the people who know most about it – you and your team! However, it is an important component to staying in business, but so is profit.

### Understand your business and your profit and loss

It’s a sad fact that most view the world through one prism...their own. To make a good business case, you must have a sound knowledge of your business and what sits behind the profit and loss and balance sheet. Unless you do, you will not be able to use the right language and you will be unable to assess the impact of your decisions and recommendations on the bottom line. QA’s credibility is damaged when they add cost for no obvious return on investment. For

Continued

## How to Get Your Message Across and Make Things Happen



example; that extra check signature, the extra approval step, the extra sample, the additional SOP. All add cost and complexity. The credibility of QA is further eroded when risk (fear) is used as the primary driver. When the consequences of not doing something fail to materialize (usually the case in my experience), respect is lost and people stop listening. When presenting proposals, make sure you are numerate and quantify the benefits. The return on investment:

- Faster or reduced testing?
- Fewer repeat deviation incidents?
- Fewer unnecessary check signatures?
- Less reworking or reprocessing?
- Less work in progress?
- Reduced cycle time?

If you just have a purely compliance-driven case, go back to the drawing board. If what you're proposing is adding cost and slowing things down, why should anyone listen?

### Ban the term 'zero risk'

Although linked to the above, this is worth a special mention. The "risk card" is often played when there is no quantifiable return on investment. You know, the "If we don't do this, we are at risk of regulatory censure" type of conversation. This is often given credence in a culture of risk aversion where zero risk is used as an excuse for not actually thinking. We all know zero risk doesn't exist and is the single biggest contributing factor to increased costs, complexity and (paradoxically) increased risks!

### Establish a strong network of contacts across the business and learn from them!

In my experience, everyone wants to do the right thing and they make the best decisions available to them based on what they know. To present a good business case, you need to understand your business and its customers. It makes great sense to better understand the roles of the teams around you – starting with your true customers. In our case, these are (usually) the wholesalers, hospitals and prescribing doctors (usually accessed through a co-operative sales colleague). I cannot over-emphasize the value of understanding the sales and marketing activity and the task it has of growing sales.

Within your organization you should understand exactly how to put together a business case which is straightforward and as simple as possible – and shows benefits in real terms, i.e. NOT based on fanciful assumptions of savings! The business case should include a couple of options, one of which you will prefer for good reasons – set these out so that the risk and benefits are clear to understand.

It will help if you work closely with colleagues from:

- Sales and marketing
- Finance
- Procurement
- Human resource
- Business development
- Regulatory

This networking and inclusive approach will have the extra benefit of gaining more support from the senior leadership team.

### Move away from reactionary firefighting to more strategic, value-adding thinking

I can remember my time when, as a middle-ranking manager, most of my focus was firefighting. Dealing with the here and now. This is when fear-driven decisions predominate and are usually counterproductive. My advice would be to plan and think more strategically, not reactively. Focus on proposals that provide real business benefits such as:

- Moving to a more risk-based approach to assess the robustness of your processes and devising continuous improvement activity to reduce that risk
- Educating your production and engineering colleagues (these groups have the biggest influence on quality) in how to conduct simple and focused self-inspections to drive continuous improvement
- Rewarding and celebrating success within this continuous improvement activity
- Simplifying your batch records to improve cycle time and reduce errors
- Taking a risk-based approach to environmental monitoring
- Moving from planned maintenance to reliability centered maintenance

### Focus on preparation, not presentation

As a senior manager, I have listened to a lot of presentations and proposals for change. I never ceased to be amazed by the lack of planning and preparation. My advice is to focus more on the planning and less on the presentation.

- Make sure you consult widely with all key stakeholders (your network), creating support in advance to avoid big surprises
- Understand your numbers inside out and keep them simple and based in reality
- Present a recommended solution with at least one alternative, explaining why your preferred option is the stronger or best solution

### Publicize your success

One final point, often forgotten. Tell everyone about your successes and how your actions have improved business performance. Report the results over the following period. If those results are good, then celebrate. If they are not, demonstrate what can be done to recover the situation and identify the learning points. Use your experiences to improve your credibility so your audience is even more supportive of your proposals and ideas the next time around.

*Martin: One final point, Frank. On my first day as a fresh faced Quality Assurance Officer, I was greeted by the plant manager, a real straight-talker. Once pleasantries were exchanged, he said to me "Just remember, I make the product that generates the revenue that pays you. You (QA) are an overhead." Was he right?*

*Frank: The answer is yes and no! For those companies with a compliance driven, zero risk culture where QA is the owner of quality and the quality management system, your colleague was right. QA was seen as a cost sink. Twenty years ago when money was no object, you could get away with this type of behavior. Companies that still have this dated attitude today simply won't be around in the future. For companies that use their quality management system to improve their competitive edge, the answer is an emphatic no.*





John Johnson (NSF Health Sciences Executive Director) responds to questions from the **Ask John** series and shines a light on some important bedtime reading.

# Expert Corner

## What Can We Learn From Quality Management Systems In Other Industries?

Why is it that we often view the pharmaceutical quality system as somehow distinct and separate from the approaches taken in other manufacturing industries? What are we missing by not studying the architecture and content of quality systems in, for example, the nuclear, “fast-moving consumer goods”, and automotive industries? Would we be able to take an insight from a world-class company, even if it wasn’t a firm identifiable with pharma manufacturing?

The question which got me thinking about this was:

**“If there was one book that influenced your perspective on how to design and monitor a quality management system, what was it?”**

As part of my professional development as a QP and Quality Leader, gaining insights from some of the most influential thinkers in quality management has been critical in helping me to determine the proportions and performance required of a local pharma quality system. Of course, the classic reads from Joseph Juran and James Collins are part of the staple diet; but what stood out for me was Jeffrey Liker’s book, “The Toyota Way: 14 Management Principles from the World’s Greatest Manufacturer.” I had the honor of spending time with Liker in 1998 during a tour of the UK and what impressed me most was how the key learnings were:

- Easily transferable to the pharma industry
- Based on reducing the risk of quality defaults and as a consequence on reducing cost and scrap product
- Illustrated with real-life shop floor case studies that showed how the key principles could be applied in practice

The principles are grouped under the key headings of:

- Maintaining a quality philosophy

- Using process thinking to resolve issues
- Adding value to the organization by developing people and partners
- Creating a learning organization by understanding the root causes of key issues through relentless challenge and reflection

When I reflect on the key concerns of the regulatory bodies, distilled from intimate knowledge of FDA warning letters and MHRA referrals to the Inspection Action Group, the recurring themes are:

- Failing to install a pharma quality system that is shown to be insightful, easily interpreted, noticeably in place, sustainable and proportionate; and by consequence the quality culture or mindset will be misplaced or under-performing
- Failing to install processes that are risk based, scientifically derived, logical and clearly defined
- Failing to invest the time and effort in professional development within the company and with suppliers, and failing to grow leaders and subject matter experts so that no organization relies on a single individual
- Failing to understand the most probable root cause of GMP deviations and misinterpreting the consequences of failure; such that expensive, unreliable and misplaced CAPAs are then applied in error, which is later evidenced by recurring failures as the CAPA is shown to be ineffective.

It is depressingly common that the four issues described here often contribute significantly to the onset of serious regulatory action; leading to cost, drug shortages, lost reputation and lost revenue.

So my simple advice is, get a copy of The Toyota Way and judge for yourself how well your company performs against the 14 management principles within it (see box alongside):

Theme	Toyota’s Management Principle	Your Pharma Quality System	Score: High 9 Medium 3 Low 1	
Develop a long-term philosophy	1	Base your management on long-term philosophy, even if in conflict with short-term financial goals	Quality policy, vision/mission/values, mid-/long-term objectives in growing a long-term, sustainable business	
	2	Create process flow to ensure problems are detectable	Management review, key metrics, use of insightful product quality reviews, real-time trending, root cause analysis techniques	
	3	Use “pull” systems to prevent overproduction	Sales and operational planning process, inventory management, amount of material as “work-in progress”	
	4	Level out the workload; work like the tortoise not the hare	Understanding resource planning, contingency planning, successor management, development of standard processes, sharing the strain across teams	
	The right process will produce the right results	5	Build a culture of stopping to fix problems once and for all	GMP deviation process, root cause analysis, CAPA effectiveness checks, knowledge management
		6	Standardized tasks drive continuous improvement	Accuracy, readability, logic and accessibility of SOPs, use of process flow charts, service level agreements and performance measures
		7	Use visual control so that no problems are hidden	Daily huddles, workplace performance indicators, management of critical process parameters, risk management and prioritization of key resources
		8	Use only reliable and thoroughly tested services and technology	Vendor assurance, lifecycle approach to qualification and validation studies that ensures predictable performance, focus on calibration and planned maintenance
Add value to the organization by developing its people and its partners	9	Grow leaders who thoroughly understand the work and who can teach others the same skills	Continuing professional development, ‘Train the Trainer’, management skills, long term investment in staff through thorough selection, onboarding and ongoing development	
	10	Develop exceptional people and teams who embrace the quality principle	Reward and recognition, objective setting and appraisal through qualitative and quantitative measurement, mentoring, employee engagement	
	11	Respect your extended network and engage them in the quest for quality	Vendor and contractor relationships, technical agreements, complaint/issue resolution, building relationships not just financial transactions	
Continuously solving issues using root cause analysis	12	Go and see for yourself (“Gemba” meaning “real place”)	Use of Ishikawa, 5 whys, is/is not, HACCP/HAZOP, issues seen as opportunities for deepening understanding of the products & processes, shop floor not office-based solutions	
	13	Make decisions slowly and thoroughly by consensus, then implement rapidly	Change control committee, management review and deviation investigation is thorough and multidisciplinary but very rapid (<5 days)	
	14	Become a learning organization	Spend your training budget wisely, always seeking a return on investment, broadening and deepening expertise ahead of crises	

Grand Total

So, once you have added up your scores from the table:

- If you scored less than 84, breathe hard and think through what you need to do to improve your organization’s quality culture.
- If you scored less than 50, I am guessing that you already feel pretty uncomfortable and need some urgent help!

**Keep your questions coming in and I’ll respond directly to you and, for selected topics, reply here in the Journal.**

### Words of Wisdom

“Anyone who stops learning is old, whether at 20 or 80. Anyone who keeps learning stays young. The greatest thing in life is to keep your mind young.”

Henry Ford

Email your questions, remarks or words of wisdom for our Expert Corner to [AskJohn@nsf.org](mailto:AskJohn@nsf.org)

# 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

### Clinical Trials Regulation Published and Expected to Go Live in May 2016

The new Clinical Trials Regulation 536/2014 was published in the Official Journal of the European Union on May 28, 2014. This new clinical trials regulation will replace the CT Directive 2001/20/EC. It will become effective six months after the new European Medicines Agency's (EMA) Web portal for clinical trial submissions goes live, but not earlier than May 28, 2016.

In addition to the changes detailed in the last edition of the Journal, these are some of the GMP implications of the new regulation that are worth noting:

- Non-investigational medicinal products (NIMPs) will be "auxiliary medicinal products" and so will not encompass non-medicinal agents; e.g. food supplements or chemicals
- The exemption from the need to hold a manufacturing authorization (MIA) is extended to include manufacture of diagnostic radiopharmaceuticals
- Investigational medicinal product (IMP) manufacturing sites that do not have to hold an MIA also appear to be exempt from need to follow Good Manufacturing Practices (GMPs)
- The Qualified Person (QP) is only required to certify product as meeting EU GMP, not contents of the clinical trial application (CTA)
- There is no possibility of opting out of some labeling requirements (e.g. expiration dates) if interactive voice response systems (IVRS) are used

- The inspecting country needs to tell others about an inspection taking place via the EMA portal

It would appear that Annex 13 of the EU GMP Guide will have to be revised as in some respects (e.g. labeling requirements), the current version is not in alignment with the new regulation.

### QP API Declaration Template Published in June 2014

The final approved versions of the active pharmaceutical ingredients (API) QP declaration template and the accompanying guidance, dated May 21, 2014, were eventually published in early June 2014.

The guidance that was published by the EMA to accompany the declaration template states:

*"... a QP declaration is required from each registered EEA manufacturer and Importer Authorisation Holder (MIAH) that uses the active substance as a starting material and/or is responsible for QP certification of the finished batch of a human or veterinary medicinal product."*

API manufacture includes complete or partial manufacture, import, dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or relabeling as carried out by a distributor of an API.

MIAHs using the active substance as a starting material and/or QP batch certification sites should:

- Verify the GMP compliance for each registered active substance manufacturer, even if this site is not routinely used. This verification should include an on-site audit by a suitably trained and experienced person, who may be a third-party contractor

- Define and fully understand the supply chain and verify that active substances used in the manufacture of medicinal products have been sourced through this supply chain
- Where the MIAH is not directly responsible for audit of the active substance manufacturing site(s), the QP of the MIAH should ensure that appropriate technical arrangements/agreements are in place with the companies responsible for such audits

The template is divided into five parts:

**Part A:** Concerned active substance manufacturing sites

**Part B:** Manufacturing/Importer Authorization Holder(s) (MIAHs) to which this QP declaration applies

**Part C:** Basis of the declaration

The QP is to tick to confirm that an on-site audit of the API manufacturer has occurred, then complete a table listing:

- The MIAH site (or contract giver)
- The auditing body (contract acceptor)
- The site audited
- The date of the last audit

If the date of the last audit is more than three years ago, this has to be justified.

There is also an optional supplementary information section.

**Part D:** QP declaration

Requires the QP to declare that:

- I am a QP with responsibility for GMP compliance of the active substance manufactured at the sites listed in Part A and am authorized to make this declaration

- The audit report(s) and all other documentation relating to this declaration of GMP compliance of the active substance manufacturer(s) will be made available for inspection by the competent authorities, if requested
- The API sites are compliant with EU GMP
- Audits were performed by properly qualified and trained staff
- Where declaration is made on behalf of multiple QPs, the guidance has been complied with

**Part E:** Name and signature of QP responsible for this declaration

Requires the QP to provide his/her name, sign the declaration and provide the MIAH site and number.

### Falsified Medicines Directive (FMD) Implementation – Introduction of Logo

On June 24, 2014 the European Commission introduced a logo that will allow patients to identify authorized online pharmacies providing authentic medicines. The logo will



appear on the websites of legally operating online pharmacies in the European Union (EU) and will link to the national competent authority websites where all legally operating online pharmacies in their respective countries will be listed.



## US News

### Drug Quality and Security Act Implementation – Identification of Suspect Product Notification, Issued June 2014, Live in January 2015

Draft Guidance for Industry: Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification was issued June 11, 2014. Other DQSA implementation standards, guidance and pilot programs will follow. This draft guidance applies to trading partners, manufacturers, repackagers, wholesale distributors and dispensers.

The DQSA requires that starting January 1, 2015, any company that determines that a product in its possession or control is illegitimate must notify FDA. So by this date trading partners must have systems in place that enable them to quarantine suspect product, conduct an investigation and determine if product is illegitimate.

This draft guidance identifies scenarios that could increase the risk of suspect product entering the supply chain and makes recommendations on how to identify the product and determine if it is suspect. It is designed to assist trading partners in complying with DQSA expectations.

Potential scenarios for increased counterfeit risk are:

- Trading partners & product sourcing
  - ◆ Purchasing from a new source
  - ◆ Receiving an unsolicited sales offer from an unknown source
  - ◆ Purchasing from the Internet from an unknown source
  - ◆ Purchasing from a source known or suspected to be of concern
    - » Involved in business transactions where illegitimate product was sold
    - » History of problematic or potentially false transactions
    - » Reluctance to provide transaction history or pedigree
    - » Transaction information or history appears to be incomplete or suspicious
    - » Identification of suspect product
- Supply, demand, history and value of the product
  - ◆ Product in high demand on the US market
  - ◆ Product with high sales volume or price
  - ◆ Products that have previously been or are currently targets of counterfeiters
  - ◆ Products currently or previously the subject of drug shortages
  - ◆ Products that have been the subject of a counterfeit or cargo theft alert
- Appearance of the product
  - ◆ Package or container used for transport appears suspicious
  - ◆ Packages using foreign terms (identification other than the NDC (National Drug Code))
  - ◆ Packages missing information (lot number, lot identification, expiration date)
  - ◆ Product that seems suspicious (wrong color, shape, unusual imprint, unusual odor, or signs of poor quality)

The draft guidance makes recommendations on how to ID suspect product:

- Be alert for offers and sales that are “too good to be true”
- Closely examine the package and transport container
- Closely examine the label on the package or the label on the individual retail unit

# Case Study: Autoclave Problem – Interpretation of Autoclave Charts

From Page 9

The slow rise to temperature of some probes is clear evidence of the presence of air.

- The heat-up stage of the cycle is not shown, so we cannot tell how long it took for other probes to reach temperature, nor can we tell what air removal processes (vacuum purges, etc) were used (if any!).
- Even at the end of the cycle, there is still a 2° difference between the temperature in parts of the load and the chamber. These should be coincident.
- The use of  $F_0$  calculations is not appropriate for porous loads. This shows only that temperature has been achieved, not whether there has been effective steam penetration. In this case, the temperature has clearly been reached only by conductive heating. To reach 121°C for 15 minutes, the steam set point has been raised to ~128°C and the cycle time has been increased.

The fundamental problem is the complexity of the assembly to be sterilized. Your options might be to:

- Redesign it
- Split it into several parts (but this would require aseptic assembly!)
- Increase vacuum pulsing and/or dwell times
- Use larger vent filters



by Martin Lush,  
President, NSF  
Health Sciences  
Pharma Biotech



## Next Steps

If you enjoyed this problem solving case study, consider attending our course, Good Autoclave Practice, October 22-24 in Amsterdam. We'll provide you with a very practical and comprehensive understanding of everything you need to know about autoclaves: the science, the principles, the practice, how to optimize autoclave performance and what to do when things go wrong. Now in its 15th successful year, this course is taught by tutors with over 75 years of combined experience.

Contact us on **+44(0)1751 432999** or email **pharmamail@nsf.org**



# News...



## New Business Development Manager Joins NSF Health Sciences – Martin Krainz

The Pharma Biotech division of NSF Health Sciences has recently added Martin Krainz to its Business Development team. Martin has a strong background in sales and marketing and has worked in the pharmaceutical industry for several years. Prior to NSF Health Sciences, he was Business Development and Account Manager with a German contract research organization and a UK-based clinical trial software solutions provider.

Martin will be running our business development in Europe, mainly in the German-speaking countries as well as France and the UK. He is the first line of contact for NSF's clients and helps them to liaise with our pharmaceutical GMP experts in order to meet their requirements in the areas of regulatory training and education, GMP-related audits and regulatory and technical consulting services.

## Introducing Our New Operations Manager – Julie Wainwright

Julie Wainwright recently joined NSF Health Sciences Pharma Biotech as Operations Manager for the office in Kirkbymoorside, UK. Julie manages the client liaison, course administration and office support teams. She has worked in office management roles for 28 years and, following a settling-in period, will play a more strategic role in relation to the direction the business is taking.

Before joining NSF, she worked as Operations and Business Development Manager for an independent hospital, where she was responsible for a large, diverse team. Julie also managed a complex and fast moving National Health Service contract. We are delighted to welcome Julie to the team.

## A Sad Farewell to George Gettinby

NSF Health Sciences is very sad to announce the sudden death of Professor George Gettinby, Professor of Statistics at the University of Strathclyde, on June 10. George had taught our QP6 module on maths and statistics since the inception of our QP training by David Begg Associates in 1990.



George's ability to demystify a subject that many delegates feared, to make it understandable and relevant, was the product of his encyclopedic knowledge, passion and gentle humor. Indeed, the module on maths and statistics has often been cited by attendees completing the QP series as the most surprising and life changing of all of the modules. With his self-deprecating humor, George attributed this compliment to the low expectation of delegates coming to the subject of statistics, but in reality it was due to his communication skills and his unique ability to connect with students on this difficult topic.

George will be sorely missed by all who knew him and all of us at NSF send our sincere condolences to his wife and family.

## Our President in Baltimore

Martin Lush, President, NSF Health Sciences Pharma Biotech, will be providing a keynote presentation at the 2014 PDA/FDA Pharmaceutical Quality System (ICH Q10) Workshop on Quality Risk Management at the Baltimore Marriott Waterfront Hotel in Baltimore, Maryland, November 3-5, 2014. His presentation will focus on how to get the most from the intelligent and disciplined use of Quality Risk Management to:

- Make better decisions
- Simplify systems
- Prevent problems
- Focus resources
- Share best industry practices

If you want to use quality risk management to transform your business, see you in Baltimore!

## Online Survey Feedback

Thanks to everyone who participated in April's online survey which provided NSF with valuable user feedback on our range of pharmaceutical courses, customer service and future educational development.

Key findings: **75%** of respondents prefer external training courses and **90%** believe that interaction with peers, instructors and networking opportunities were the key drivers to attending a course outside the office. A comprehensive overview of key survey findings will be presented in our December issue.

Here are the five lucky respondents who each received Amazon Vouchers (or equivalent)

- Pauline Johnstone
- Maria Bernal
- Kate Hogg
- Enrico Caponi
- Dick van Drumpt

## NSF Pharma Biotech Returns to the Seaside Resort of Rimini, Italy for the Annual AFI Symposium

The influential Italian pharmaceutical trade association, AFI (Associazione Farmaceutici Industria), hosted its annual GMP symposium from June 11-14, 2014 in Rimini, Italy and we are proud to report that NSF was prominent at this year's event with both an educational workshop and a booth to host meetings.

NSF's workshop focused on the important topic of CAPA management and was held on the opening day of the symposium. Stephen Engels, Principal Associate at NSF Pharma Biotech, based in Switzerland, took on the role of moderator with expert input from Giovanni Cosmi and Marco Budini from NSF Italia and Michele Panzitta from AFI.

CAPA effectiveness is under close scrutiny from the regulatory bodies, which led to wide attendance and much debate during the workshop. NSF Pharma Biotech intends to revisit this fundamental topic in the form of in-house training, consulting and auditing services to enable customers in Italy and the Italian speaking Swiss canton of Ticino to keep up-to-date with the subject.

New to the event this year was NSF's free prize draw for a professional training class from NSF's experts anywhere in the world. This year's lucky winner was Gloria Lecchi (Regulatory Affairs & QA Director of Ferring Farmaceutici, Italia). Congratulations, Gloria!



# Forthcoming Courses

What's planned for November – December 2014



## Our EU Career Path Key

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

## EU Courses:



### Effective Pharmaceutical Audits and Self-Inspections

An IRCA certified Pharmaceutical QMS Auditor/Lead Auditor course.

**November 3-7**

Park Hotel Amsterdam, Amsterdam, The Netherlands

**Course Fee: £2,750 ex VAT**



### Medicinal Chemistry & Therapeutics

Essential information on: The Body and How it Works – Major Disease States – Medicinal Products and How they Affect the Body – plus other relevant issues.

**November 10-14**

York Marriott Hotel, York, UK

**Course Fee: £3,350 ex VAT**

*Early Bird or Multiple Delegate discounts apply to some of our courses. Please visit our website, [www.nsf.org](http://www.nsf.org), for full details.*

*If you think training is expensive, try ignorance*



### Pharmaceutical Quality Systems: Best Industry Practice

How to achieve operational excellence through simplification.

**November 11-13**

Renaissance Manchester City Centre Hotel, Manchester, UK

**Course Fee: £1,910 ex VAT**



### Pharmaceutical GMP

Europe's most popular GMP course!

**November 24-27**

Park Hotel Amsterdam, Amsterdam, The Netherlands

**Course Fee: £2,550 ex VAT**



### Good Distribution Practice

A practical interpretation of new guidance.

**December 2-3**

Manchester Marriott Victoria & Albert Hotel, Manchester, UK

**Course Fee: £1,470 ex VAT**

## US Courses:

### Effective Pharmaceutical Audits and Self-Inspections

An IRCA certified Pharmaceutical QMS Auditor/Lead Auditor course.

**November 3-7**

Boston Marriott Cambridge, Cambridge, MA

**Course Fee: \$3,200**

### Pharmaceutical Quality Systems for R&D

The proven blueprint for a phased approach to quality management systems implementation.

**November 11-12**

NSF Health Sciences, Boston, MA

**Course Fee: \$1,775**

### Deviation and CAPA Workshop

Benchmark your processes and procedures in the context of industry best practices, regulatory requirements, and identify opportunities for improvement.

**November 13**

NSF Health Sciences, Boston, MA

**Course Fee: \$500**



### Managing Investigational New Drug (IND) Supply and Assurance

A comprehensive review of regulatory requirements for Clinical Supplies manufacture in the USA, Europe and key markets including China and India.

**December 2-4**

San Mateo Marriott San Francisco Airport, San Mateo, CA

**Course Fee: \$2,950**

### NSF HS Education Programs WEBINAR

Showcase of examples and best practices used by NSF to creatively achieve course objectives with adult learners

**December 11**

10am EST

**Course Fee: FREE**



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

#### Words of Wisdom

Chief Financial Officer

*What happens if we train all these people and they leave?*

CEO

*What happens if we don't and they stay?*

For more information [www.nsf.org/info/pharma-training](http://www.nsf.org/info/pharma-training)

Book your place at [www.nsf.org/info/pharma-training](http://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.



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](http://www.nsf.org/info/pharmabiotech)



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