Journal

2018, Issue 42

"Why Did My Plant Close?"

THE VITAL IMPORTANCE OF WINNING THE TALENT WAR AND INVESTING IN EDUCATION

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welcome

It's All About Your People

I spend a lot of time in hotels. One of my favorite choices is a well-known budget chain. They don't have the fancy bars, restaurants, gyms or loyalty points and are usually located close to a motorway or tucked away on an industrial estate somewhere. But they are always clean and eight out of ten times (nothing ever is perfect) the staff are genuinely warm, smiling and pleased to see me. Contrast this with a recent stay at a four-star airport hotel where the check-in staff were utterly miserable, bordering on rude. I did some more research into how each chain recruited, trained and retained its staff. Guess what?

- The budget chain focuses on personal likeability and emotional intelligence, not qualifications. Their selection process is more rigorous than their four-star counterparts. Psychometric tests, role plays… you name it. All challenging emotional intelligence, resilience and likability. "We need to know how they will greet a stressed and tired guest at 3am," I was told.
- The budget chain also invests more in education and, vitally, mentorship.
- They also retain their staff. After all, why would you leave a happy workplace that invested in your personal development?

Issue 42 of The Journal has a very strong people focus. If you're feeling sleepy, please read **"Why Did My Plant Close?"** (page 3). If this doesn't wake you up, nothing will. If you don't attract and retain the very best talent, you won't stay around for much longer. Getting the best from your people is also the theme for Jim's article on how to change workplace habits (page 6). There is an old saying that if you're not developing, you're dying. If you want to grow, immerse yourself in John's walk-through **organizational development**. He makes it sound simple (page 8)! Catherine's explanation of our **blended eLearning** programs (page 10), the **opening of our state-of-the-art training facility in Hamburg, Germany** (page 19) and the launch of our **second MBA-style program in India** (page 22) will give you a sense of how NSF continues to grow and develop to meet your needs. However, if I'm perfectly honest, the best part of the Journal is on page 18 where you will find out what our team gets up to helping those in need in local communities. Humbling indeed.

Finally, for those of you in need of a Brexit (what next?) fix, take a deep breath and go to page 11.

Anyway, I'm off to another hotel. No prizes for guessing which one.

Martin Lush

Martin Lush,
Global Vice President, Pharma Biotech
and Medical Devices, NSF International

"Why Did My Plant Close?"

by Martin Lush, Global Vice President, Pharma Biotech and Medical Devices, NSF International

The Vital Importance of Winning the Talent War and Investing in Education

I recently had a meeting with a CEO to help solve his company's pain points. He was in need of a big dose of a strong analgesic. Falling prices, suffocating complexity, poor product development, supply chain disruption, product shortages, increasing operational costs and unhappy investors were taking him beyond his pain threshold. One pain point jumped off the screen: poor recruitment and retention. They had an attrition rate of 14 percent.

"We just can't find good people," he said.

I told him he wasn't alone.

Top Three Roadblocks to Finding the Right People

1. **Exam obsession is dangerous!** Most educational systems are obsessed with teaching to the test. Our industry is at risk from a future workforce who can pass exams but struggles with what's needed most – excellence in problem-solving, and critical and creative thinking where high emotional intelligence is more important than IQ. When we teach to the test we kill the passion for learning. For our industry to prosper we need an agile workforce; a workforce of enthusiastic *lifelong* learners with the ability and passion to master news skills quickly.

   Exam obsession also engrains a dangerous behavior, *fear of failure*. Teaching to the test installs a belief that only perfection (the right answer) is acceptable. In this imperfect world where 'failing fast' is key, we need a workforce (and a culture) comfortable with failure. People who use failure as an automatic springboard to more creative, innovative solutions. If we are to succeed, failure must be embraced, not feared.

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2. **The demographic time bomb is about to explode.** How dependent is your company on loyal Baby Boomers (born 1945 – 1964)? This demographic group makes up most of the global workforce, but now for the scary part, most will have left full-time employment by 2025. How much knowledge and experience is about to walk out the door? It gets scarier. Falling birth rates will mean fewer people to replace them. The War for Talent hasn't even started yet.

   Your company's future depends on other generational cohorts. Generations Y (1980 – 1995) and Z (born after 1995) who, immersed in a world of social media, have different social habits that could dramatically alter your workplace and working practices.

3. **India and China are educational powerhouses**. It's a numbers game. With a joint population of 2.8 billion by 2020 and 3 billion by 2050, India and China will be the talent pools of the world. Indian universities produce 1.5 million engineering graduates every year. By 2025, 85 percent of STEM (science – technology – engineering – math) graduates will come from India and China.

So, what's the big deal?

In this VUCA (volatile, uncertain, chaotic and ambiguous) world, successful companies will be different from the rest. They will:

- Have a **high trust culture** across their supply chain from top to bottom
- Have a learning through mistakes culture and allow their people to **fail fast**
- **Never accept the status quo**, encouraging people to challenge rules, not blindly follow them
- **Fix problems and make decisions** by those closest to the action, not by management
- Excel at **brutal simplification**
- Be **risk smart**, not risk averse

We all know our products and services are only as good as our people. Those who can master these essentials will be in very short supply for two reasons. The first one has already been covered. Most educational systems teach to the test, not how to think. Secondly, our industry doesn't invest enough in teaching people how to solve problems and think critically and creatively.

In short, successful companies will embrace the reality of a chaotic, 'boom and bust' world and plan for it by recruiting and developing an agile workforce.

Winning the Talent War: How to Stay Open for Business

1. **Keep your Baby Boomers** (and their legacy knowledge and experience) for as long as possible. This will mean adopting more flexible working practices to entice them to stay. You must then invest in mentorship programs that allow them to spend 30+ percent of their time coaching and mentoring leaders of the future.
2. **Brutally delegate… and expect mistakes.** To develop people, you must let go and allow them to fly solo. When they crash, and they will, focus on lessons learned - not punishment.
3. Make sure your **recruitment process focuses on values and talent**, not exam grades. Focus on the who, not the what. You can teach the rest. Challenge aptitude and expertise in what matters most for your future:
   - > Creative and critical thinking. Ask them about their thoughts on De Bono, Claxton, Buzan and other 'thinking' experts.
   - > Risk-based decision making. Get them to describe their decision making process. Give them some risk scenarios.
   - > Problem-solving. Give them a problem to solve. Getting to the right answer is not the goal. It's about the process they used. Were they systematic and data driven? More logical than emotional?
   - > The ability to spot patterns and trends in data. Gone are the days of moving data to authority for a decision. We must now move authority to the data for fast analysis and decision making.
   - > Emotional intelligence. Look for people who are naturally open-minded and comfortable with thoughtful disagreement. People who can naturally get beyond disagreement.

Make sure your in-house education programs are developing these skills and talents to the next level and beyond to achieve institutional mastery. Your future depends on doing these to Ph.D. level. Just focus on finding the talent (not the qualification) and developing it. Remember, you are hiring people for the future, not the here and now.

4. **Take a walk on the wild side. Stop your obsession with BScs, MScs and Ph.D.s** as entry requirements. A lot of very intelligent and talented people don't go to university. Look to recruit talent from other industries. If you want expertise in the supply chain, hire from fast-moving consumable goods. Want good problem-solvers? Take a look at the automobile sector. Once you've got the non-pharma talent, be open to their ideas and suggestions. Don't slam the 'compliance' door in their face.
5. If you are based in the EU or the Americas, **establish strong relationships with the top Indian universities.** This is your future talent pool.

And a reminder for our governments and policy makers:

- > When creating education policies, please talk with industry first.
- > Any society that is allowed to undervalue the importance of teachers is making a perilous error. Teachers and educators should be the best of the best and rewarded accordingly.

And finally:

"Democracy can't succeed unless those who exert their choice are prepared to choose wisely. The real safeguard of democracy, therefore, is education". FD Roosevelt.

Amen to that.

by Jim Morris,
Executive Director,
Pharma Biotech,
NSF International

The Effect of Cognitive Load and Habit Formation in Pharmaceutical Plant Operations

NSF's pharma biotech team is committed to developing tailored programs that make a difference. We teach fundamental skills/knowledge and link these to leadership objectives such as driving down repeat deviations, simplifying SOPs or increasing the knowledge and risk awareness of first line supervisors. We deliver enjoyable, highly interactive programs that impart knowledge in a meaningful way. If there is a common thread in many of our client requests it relates to reducing variability and simplifying operations. In that vein, there are two concepts we frequently employ; cognitive load and habit formation.

COGNITIVE LOAD

Cognitive load is the amount of information we can process at a given point in time. Some people have greater capacity than others and their capacity will vary with the time of the day – some people will process better in the early morning versus others late morning, etc. And while we cannot necessarily control the individual capacity of our personnel, we can control the distractions around them.

Each distraction, whether a cell phone, email, or multitasking, impacts cognitive load. The more distractions, the greater the impact and the less cognitive capacity we have for performing the task at hand. If that task is attending to an equipment set-up, calculating the reconciliation of components in the batch record, or simply taking down instructions from our supervisor, what is the risk that the task is executed incorrectly? As cognitive load goes up, the risk of incomplete or incorrect task execution also goes up. See *Figure 1*.

HABIT FORMATION

Habits are formed through repetition, plus they are often anchored by our emotions. The MAtH principle provides us with the sequence of Motivation – Ability – trigger – Habit. We need the three precursors – motivation, ability and the trigger – for a habit to be formed. See *Figure 2*.

The motivation can be as simple as working with a subject matter expert (SME) and understanding WHY a task needs to be carried out. If our training is carried out by our SMEs, we form an emotional connection and a desire to respect the knowledge imparted by the more experienced individual. We are each motivated differently; however, the beauty of the manufacturing environment is that we are often motivated by our peers and the people whom we look up to.

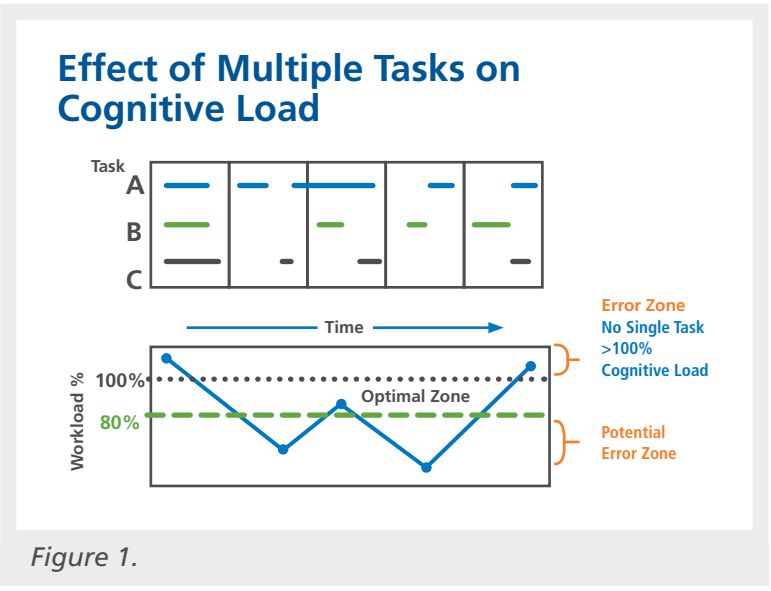


Figure 1.

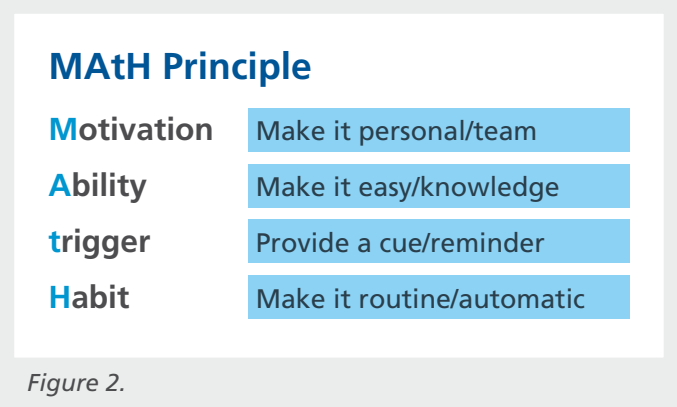


Figure 2.

OUR CHALLENGE

The challenge we have in most operations is that we do not respect cognitive loading and we do not offer people the opportunity to develop habits. Therefore, as you plan your work, consider the optimal loading of people. If the loading is too high or too low, we will see suboptimal performance. Find that sweet spot! Secondly, along with optimal loading, it is important to think about habit formation, particularly for the most critical tasks. The vast majority of pharmaceutical operations are still in the read-and-understand mode of SOP training. One head of learning and development at a large biopharma manufacturer estimated that their company devoted 3.5 million hours annually to read/understand training and estimated that only 10 percent of the information is retained. This is a recipe for disaster; not to mention the loss of efficiency! And, frequently, procedures are issued just in time for use and the time available to train is virtually gone.

The best practice I have seen in certain biologic operations is to build the training into the calendar and ensure that competency is verified in a proactive way. This does not simply mean that a written assessment is carried out to confirm comprehension. An assessment is helpful and provides some measure of knowledge acquisition. However, we must go further. For the most critical tasks – such as filter integrity tests, sampling steps, pH adjustments – we must verify competency. And, this is not a one-off exercise. The habit is formed with repetition. Therefore, for someone to carry out a filter integrity test they must demonstrate competency through repeated and successful execution of the task. The number of repeats will be a function of the task complexity and adeptness of the person taking on board new information (cognitive load). As in aviation it's the flight time or time on task that counts!

In conclusion, as we think about training and education in pharmaceutical plant operations, think about:

A. Optimal loading of your personnel; this impacts their cognitive load and potential error rate

B. The formation of habits through PLANNED repetition in a safe/supervised environment

C. The verification of competency through repeat verification

If you believe you can change – if you make it a habit – the change becomes real. This is the real power of habit; the insight that your habits are what you choose them to be. Once that choice occurs – and becomes automatic – it's not only real, it starts to seem inevitable.
C. Duhigg, The Power of Habit.

If you have any questions or require assistance, don't hesitate to contact us at **USpharma@nsf.org** or **pharmamail@nsf.org**.

by John Johnson,
Vice President,
Pharma Biotech,
NSF International

What Does the Term **Organizational Development** Mean to You?

When NSF conducts research or support projects that seek a level of transformational change within a team or wider organization, we apply our experience and expertise in the internationally recognizable current Good Manufacturing Practice (cGMP) expectations. We then run proven processes that we know work well or can be adapted to work well in any circumstances. In our industry, there is no substitute for a deep knowledge and broad experience in how to interpret and apply the cGMP expectations in practice at the workplace.

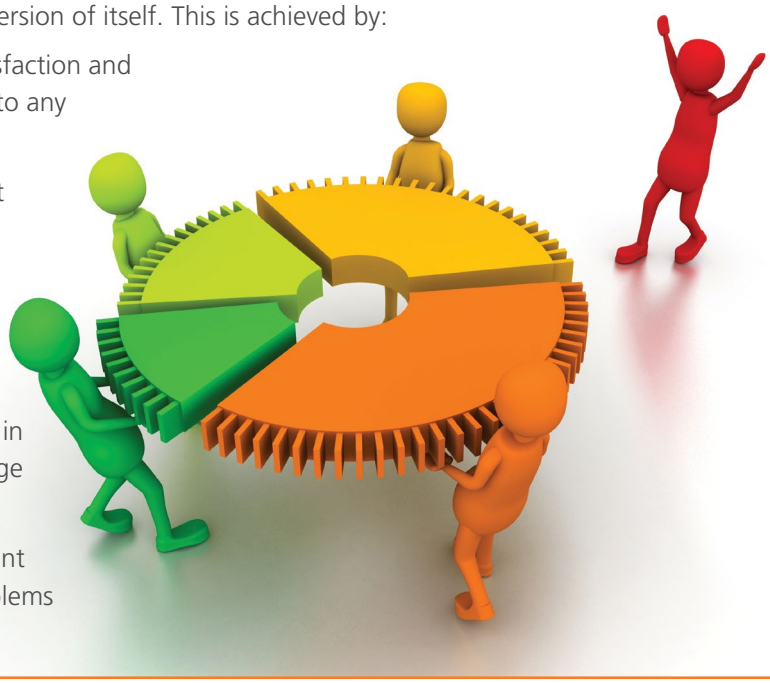
However, can this alone be relied on to drive the type of changes that are often sorely needed?

Why do projects that simply rely on cutting and pasting the regulations into a client's pharmaceutical quality system rarely provide perpetual compliance to cGMP?

Why is it that many firms, who have documented and instructed on a comprehensive set of policies and procedures, still never achieve the level of business performance or risk management that the market expects? In other words, you may have the best set of policies, procedures and records, yet still not meet cGMP and still suffer unpredicted costs, supply chain issues and GMP non-conformance.

Kurt Lewin of the Massachusetts Institute of Technology was instrumental in changing the way we think about change management, and how we can ensure our teams and individuals are set up, encouraged and coached for success. His work in the 1930s and '40s led to a growing interest in how to engage individuals and large teams to work together in a way that allows the organization to be the best possible version of itself. This is achieved by:

- Increasing employees' level of satisfaction and commitment by improving buy-in to any change needed.
- Improving a team's ability to predict and confront problems rather than neglecting them, and to manage conflict collaboratively each time in a way that grows trust and cooperation within the team.
- Increasing the organizational skills in problem-solving through knowledge management and education.
- Engendering a spirit of improvement (without painful regret of the problems in the past).



Focusing on the long-term ability and collaboration of the team, while minimizing short termism or snap judgements, led to some startling improvements in industrial productivity during the 1950s and '60s, acting as a catalyst for the total quality movement. **The big difference was that the focus was squarely on the most important aspect of any organization; its people and their ability to make the right decisions at the right time for the right reasons.**

So, what does organizational development do for you in practice?

- It helps define a communication link that gives team members a reason for caring and for getting involved in change (see also NSF's webinar on behavioral aspects of GMP – visit our resource library at **www.nsf.org/info/pblibrary**).
- It uses that engagement to break the stereotypes or assumptions that hold back a team from achieving more from its finite (and often shrinking) resources and budgets.
- It helps organizations define its values, so that 'true north' is maintained even when a storm is brewing.

Critically for us, it makes sure that the required changes to be made (whether during upsizing/downsizing, acquisitions/divestments, technology transfers or GMP remediation projects) are always rigorously defined using diverse perspectives and then executed flawlessly for the clear good of the organization. Without organizational development, changes planned can often be short lived, unloved and unsustainable. Of course, any change needing constant rework will add cost, creating mistrust and possibly impacting team confidence and momentum.

The key message is to make organizational development an important factor in plotting your team's progress and in helping them take the collective foot off the brake and onto the accelerator!

NSF's Pharma Biotech Team Moves Toward Blended Learning Approach with eLearning

by Catherine Kay, Director, Pharma Biotech, NSF International

To support and complement the face-to-face training programs offered by NSF's pharma biotech team, we launched our eLearning program in April 2018.

Currently available modules include short sessions of no more than an hour that provide:

- An introduction or overview, such as GMP for Engineers and Microbiology: The Basics.
- More specific technical training, such as Self-Inspections, The Role of the Responsible Person and Good Inspection Management.
- Sessions targeting the quality professional for continuing professional development (CPD), such as EU Pharmaceutical Law as well as Human Error Prevention, which goes beneath the surface of issues and looks to fix the real causes of errors and mistakes.

Quite simply, eLearning is using technology to deliver training anytime, anyplace. Three great reasons to use eLearning:

- It provides the ability to communicate to and train a wide group of people efficiently and consistently in a short time.
- It offers the flexibility to learn at your own pace, any time of the day, using a computer, tablet or mobile device.
- It reduces time away from the workplace, cuts down on expensive travel and reduces the need for costly classroom-based training.

To develop these eLearning sessions, we used the knowledge of our subject matter experts and experienced designers to make the sessions engaging. The sessions include a downloadable document to print and take away key learning points, along with knowledge check quizzes and a course certificate to show completion.

New modules are in development every month – look out for Computer Systems Validation, Data Integrity, Cleaning Validation and many more!

We can also provide customized modules for your specific needs. We will be using eLearning to support several clients in the future to develop in-house training material that will be used alongside their other training methods.

Blended learning approaches use multiple methods to deliver learning, combining face-to-face interactions with online activities, whereby the online activity can be introduced before or after a face-to-face training session. This allows the time in traditional classrooms to focus on reaching the higher levels of learning such as analyzing and evaluating. It has been shown that blended learning results in a higher knowledge retention rate than traditional learning, as it appeals to a wider range of learning styles.

FIND OUT MORE DETAILS ON OUR eLEARNING

Please visit www.nsf.org/info/pharma-e-learning or contact us at e-pharma@nsf.org.

You can find out more about our medical devices eLearning on page 21.

NSF LAUNCHES FURTHER **QUALIFIED PERSON** TRAINING IN 2019

by Catherine Kay, Director, Pharma Biotech, NSF International

What does the future hold for the Qualified Person (QP) post-Brexit? There has been much debate on this matter.

We do know that all EU centralized marketing authorizations must be held by a legal entity within the EU and that QP certification must occur in the EU. The role of the QP is already in UK law (SI 2012-1916) and the UK is expected to retain the role of the QP post-Brexit. It does mean however that EU QPs may no longer be able to accept certification by UK QPs and vice versa. The result of all of this is that there will be a growing need for more QPs both in the UK and in the EU.

NSF has been running QP training courses for 28 years. With 177 training modules, over 4,000 delegates and a pass rate of 96 percent, we have just seen our 300th QP pass their viva! Congratulations Alan Clark, Global Technical Director & QP, Health Supply, Reckitt Benckiser Healthcare UK.

NSF currently runs 12 modules, meeting the requirements of the UK QP Study Guide, over a 21-month period. With the demand for this training increasing and delegates attending from overseas as well as the EU, additional courses will be launched from January 2019 in both London and Brighton. This will provide the opportunity for all 12 modules to be completed over a 12-month period, providing flexibility and choice of location to the delegate.

In June and September of 2018, we ran a seminar in each of our new locations, which were well attended, and we received some great feedback on the new venues. Topics covered included a pharmaceutical law and Brexit update, as well as an overview of document simplification methods and techniques. There were plenty of discussions on the challenges that industry faces; with deviations and CAPA, serialization, pharmacovigilance, data integrity and Annex 1, as some of the frequently named topics.

Modules can be taken in any order, or alternatively can be used as a stand-alone course for CPD. For those taking all modules, there will still be the opportunity to gain postgraduate qualifications, from a Postgraduate Certificate to an MSc, awarded by the University of Strathclyde.

The teaching and learning on the courses is highly interactive, using a combination of lectures, discussion scenarios and teamwork, which provide a context to help with decision making, a prerequisite for the future QP. There are also additional site visits planned to pharmaceutical manufacturing facilities in the UK to see the real-life application of what has been learned.

For more information on our QP training, visit **www.nsf.org/info/qptraining** or email **QPpharma@nsf.org**.

LYNNE BYERS' 40 YEARS IN THE INDUSTRY

Our Executive Director, Lynne Byers, celebrated 40 years in the pharmaceutical industry in July. We have taken the opportunity to interview her about her long service.

What was your first job?

My first job was as a Junior Laboratory Assistant at the GSK site in Barnard Castle, England. I spent two weeks learning how to do titrations, weighing and all the basic tests while the factory was shut down. Three of us started at the same time and we were trained in the laboratory techniques by a lady called Joan Martin. My first job was to work in the raw materials laboratory testing APIs, excipients and other raw materials such as solvents.

What major differences do you see between working in an incoming materials laboratory in 1978 and today?

Many of the tests are the same, but the techniques differ. One surprising thing is that we did not have methods then; we worked directly from the pharmacopoeias and had to work out concentrations, etc. There were also no computers, emails or mobile phones. GC and HPLC were in use, but without computers we had to measure the peak sizes with rulers and do all calculations manually. At least we had electronic calculators. There were no printouts from balances or pH meters. Everything was recorded manually, and all calculations were checked by a second person. So, there are some differences and some similarities with what still happens today. The biggest difference is the use of computing and even robots in today's QC laboratories.

Where did your career take you?

After 10 years in various laboratories and gaining my degree in chemistry, I moved to an operational quality role in an oral solid dose/ aseptic filling operation. I then started to study for my Qualified Person qualification. I even did a couple of modules of the DBA (now NSF) training course. I became Head of Quality for the cephalosporins product stream. After moving into a role managing GMP education, 'intelligence into action' and supplier quality management, I moved from the north to the south of the UK and became Quality Director for another GSK site. I then left GSK and joined the MHRA as Head of Inspectorate and Licensing. This was a fantastic opportunity where I led the UK GxP inspectorates and saw how the regulators work. After a couple of years, I moved back to industry and worked for UCB where I was responsible for global quality strategy, including developing a GxP PQS. Next GSK tempted me back and I became VP, Head of Shared Services and Supplier Quality. I then moved from the UK to Switzerland where I was appointed as Global Head (VP) of Country QA and then Global Head (VP) of External Supply at Novartis. My latest move saw me moving back to the UK and working as Executive Director for NSF. I am now living about 15 miles from where I started my career.

What advice would you give to anyone starting their career in the pharmaceutical industry?

Enjoy it. As an industry we help save and improve peoples' lives so there is a real sense of achievement. As someone who has spent all my career in quality or as a regulator, it is a privilege to work in the pharmaceutical industry. Get as much experience as possible from working in manufacturing or various parts of QA and QC.

My top 10 team event memories

The people we work with are important no matter which industry we work in.


Lynne with Martin Lush and Mike Halliday

1. A cruise on Windermere, UK.
2. River cruises on the Thames, England and Chesapeake Bay, USA.
3. A buffalo cart ride in Poland.
4. Visiting the pyramids on a business trip to Egypt.
5. Team events on the London Eye.
6. Going on a cable car to the Great Wall of China in a gale.
7. Teambuilding cooking in Paris, Singapore and Basel.
8. Being led blindfolded across a table tennis table in Switzerland.
9. Practicing a team song in a bandstand in Brighton, UK.
10. Going to a baseball match in the USA.

I would love to hear from anyone who was also at the events listed above (**lynnebyers@nsf.org**).

What do you see as interesting challenges for the industry both now and in the future?

I see a few challenges now that will probably continue in the future.

The first is how to make it easy to comply with regulations or processes. A saying I coined is "One person's perfect process is another person's bureaucracy." Sometimes as an industry we spend so long developing very detailed processes we forget the big picture and to include input from the people who need to implement or follow the processes. The challenge is to not update procedures or policies every time there is a regulatory finding, but to look for the true root causes. So often I see very complicated processes and procedures which are almost impossible to follow. The efforts to have simple yet compliant processes and procedures will continue.

The second is how to have and retain confidence in the ever-growing complexity of supply chains. So often regulators publish warning letters or non-compliance reports for companies. Customers of those companies are left with a lack of APIs or products. However, for a QA person there is often some soul searching about how did I/we miss it? What should I do now? The cooperation between regulators is very welcome and I predict an increase in that cooperation.

Personalized medicine is also a current challenge and will become more so. How should the industry manage the quality assurance of advanced therapeutic medicinal products, such as cell and gene products? How do systems ensure vein-to-vein traceability from the patient and back to that same patient? What level of risk is appropriate when the product is potentially life-saving? These questions will demand different thinking from quality professionals and the industry as a whole.

What do you enjoy doing outside work?

I like travelling and take my full holiday entitlement! This year I have been to Switzerland, Norway, Iceland, Greenland, Canada and Portugal, and am going to India in November.

I also like going to the theatre and can walk to my local theatre from my house. I am also interested in history and like visiting historical houses, castles and museums.

by Pete Gough, Executive Director, Pharma Biotech, NSF International

& Andrew Papas, Vice President of Regulatory Affairs, Pharma Biotech, NSF International

Regulatory Update

EU News

EMA Q&A on Health-Based Exposure Limits

In late April 2018 the European Medicines Agency (EMA) published its final version of a Q&A on implementation of risk-based prevention of cross-contamination in production, and guideline on setting health-based exposure limits (HBELs) for use in risk identification in the manufacture of different medicinal products in shared facilities.

This final version contains several significant differences from the draft version that was published in January 2017. The principal difference is that it no longer refers to highly hazardous products. Instead Q2 of the final version refers to a continuous scale of hazard based on HBEL-PDE, with a diagram developed from the ISPE's risk-based manufacturing guide.

The final Q&A still states that cleaning limits should not be set at the calculated HBEL. For existing products, manufacturers' historically-used cleaning limits should be retained and can be considered alert limits, provided that when taking cleaning process capability into account, they provide sufficient assurance that excursions above the HBEL will be prevented. A similar process should be adopted when establishing cleaning alert levels for products introduced into a facility for the first time.

EU GMP Annex 2: Manufacture of Biological APIs and Products

A revised version of Annex 2 was published on June 26, 2018 to make it clear that this annex is no longer applicable to advanced therapy medicinal products (ATMPs) following the publication of Part IV of EudraLex Volume 4, the separate ATMP GMP Guide, which became operational on May 22, 2018. This revised version was immediately applicable from the date of publication.

Annex 17: Real Time Release Testing and Parametric Release

The final version of Annex 17, Real Time Release Testing (RTRT) and Parametric Release, was also published on June 26, 2018 and becomes effective on December 26, 2018. In the final version, the requirement that was in the draft for the control strategy to be based on acceptance sampling has been replaced with a more scientific requirement that the "Control strategy should describe and justify the selected in-process controls, material attributes and process parameters which require to be routinely monitored and should be based on product, formulation and process understanding".

The revised annex makes it clear that "When RTRT has been approved, this approach should be routinely used for batch release. In the event that the results from RTRT fail or are trending toward failure, a RTRT approach may not be substituted by end-product testing".

EU-USA Mutual Recognition Agreement

On June 1, 2018 the U.S. FDA announced that it had determined that it could recognize a further two European drug regulatory authorities as capable of conducting inspections of manufacturing facilities that meet FDA requirements. The two additional authorities are located in Ireland and Lithuania.

This brings the total number of EU regulatory authorities recognized to 14, exactly half of the current EU Member States. A further six authorities are scheduled to be recognized by December 1, 2018 with the final eight assessments to be completed by July 15, 2019.

EMA Draft Guidance for Handling and Shipping of IMPs

In May 2018 the EMA published the document "Draft guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice".

The draft guideline lays down the principles for management of the investigational medicinal products by the sponsor for use in a clinical trial and in accordance with Good Clinical Practice which interface with, and are complementary to, Good Manufacturing Practice.

Investigational medicinal products should remain under the control of the sponsor until after completion of the two-step batch release procedure, consisting of the batch certification by the Qualified Person and the regulatory release by the sponsor for use in a clinical trial. Both steps should be recorded and retained in the clinical trial master file held by, or on behalf of, the sponsor.

Expansion of EU-Japan MRA

As a result of the signing of a new comprehensive trade deal between the EU and Japan on July 17, 2018, the scope of the existing EU-Japan mutual recognition agreement (MRA), which was first signed in 2004, has been expanded to include drug substances (active ingredients), sterile drugs and biological drugs such as vaccines.

ICH News

New Members and Management Committee Members

At the June 2018 meeting of the International Conference on Harmonisation (ICH) in Kobe, Japan, the Taiwan Food and Drug Administration (TFDA) was added as a regulatory authority member and four other country's authorities were added as observers: Armenia (SDCMTE), Malaysia (NPRA), Moldavia (MMDA) and Turkey (TITCK).

At the same meeting, several new members were added to the ICH Management Committee:

> Three regulatory authorities: China, Singapore and South Korea

> Two industry associations: International Generic and Biosimilar Medicines Association (IGBA) and the U.S. focused Biotechnology Innovation Organization (BIO)

New ICH Quality Topics

At the ICH meeting in June 2018 the management committee agreed to the formation of two new quality expert working groups and identified two other topics that will start later:

> New working groups will start immediately to:

- Revise Q2 (R1) Analytical Validation and also to write a new Q14 guideline on analytical procedure development
- Write a new Q13 Continuous Manufacturing guideline

> Topics for later:

- Drug interaction studies
- Adaptive clinical trials

Regulatory Update

Error in ICH Q3C – Residual Solvents

In June 2018 an error was identified in the calculation of the permitted daily exposure (PDE) for ethylene glycol. There was a discrepancy between the PDE for ethylene glycol mentioned in summary Table 2 and the conclusion from Appendix 5. The Table 2 value of 6.2 mg/day (620 ppm) was in error and has been changed to a PDE of 3.1 mg/day (310 ppm), consistent with Appendix 5.

Regulatory authorities have said that they will adhere to the correct PDE immediately but will discuss this case by case with their applicants.

Brexit News

The UK government has reiterated in a July white paper its desire to continue to participate in the work and systems of the EMA after leaving the EU. It remains to be seen if the EU is willing and able to accommodate this desire.

EMA Guidance

On June 19, 2018 the EMA published an update to its guidance to help pharmaceutical companies prepare for Brexit:

- Revision 3 of "Questions and Answers related to the United Kingdom's withdrawal from the European Union with regard to the medicinal products for human and veterinary use within the framework of the Centralised Procedure" added seven new Q&As, numbers 19 to 25.
- Revision 2 of "Practical guidance for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure" was published on the same day.

UK MHRA News

On March 9, 2018 the Medicines and Healthcare products Regulatory Agency (MHRA) published the final version of 'GXP' Data Integrity Guidance and Definitions. This updates the 2015 guidance, which focused primarily on GMP, to cover all GXPs (Good Clinical Practice, Good Distribution Practice, Good Laboratory Practice, Good Manufacturing Practice and Good Pharmacovigilance Practice).

The MHRA says that its 2018 GXP data integrity guidance has a high degree of alignment with documents published by other regulators such as PIC/S, WHO, OECD (guidance and advisory documents on GLP) and EMA.

U.S. News

U.S. FDA Approves Eleventh U.S. Biosimilar

Since FDA was granted the authority to approve biosimilars with the passage of the Biologics Price Competition and Innovation Act in 2009, it has approved 11 biosimilars. The first FDA approval was for Sandoz's application to market Zarxio® (filgrastim-sndz) on March 6, 2015 and the most recent on June 4, 2018 was for the Mylan-Biocon application to market Fulphila® (pegfilgrastim-jmdb). Currently FDA is tracking to approve four biosimilar applications per year based on the last three years of approvals. However, prescriber adoption of biosimilars has been slow in the U.S. and none of the approvals requested or received an 'interchangeable' designation; this would allow, in some states, the substitution for the reference product without the intervention of the healthcare provider who prescribed the reference product.

Recently, FDA Commissioner Scott Gottlieb stated "Biosimilars foster competition and can lower the cost of biologic treatments for patients, yet the market for these products is not advancing as quickly as I hoped. I believe that the FDA can do more to support the development of biosimilars, as well as promote the market acceptance of these products. As the cost to develop a single biosimilar product can reach hundreds of millions of dollars, it's important that we advance policies that help make the development of biosimilar products more efficient, and patient and provider acceptance more certain". This statement was in response to the recent withdrawal of the FDA draft guidance Statistical Approaches to Evaluate Analytical Similarity on June 21, 2018.

The withdrawal was based on public comments that could potentially reduce the cost and increase the efficiency of biosimilar development.

The main takeaway for this administration is that biosimilars are being developed and commercialized but U.S. adoption is slow to date and FDA is looking to facilitate their approval and adoption within the constraints of its mandate.

FDA Issues ICH Q12 for Comments – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management Core Guideline

Originally endorsed on November 16, 2017, this ICH consensus draft guideline by the ICH Expert Working Group is at step 2 of the ICH process, and was transmitted to the regulatory authorities of the ICH regions for internal and external consultation according to national or regional procedures. Therefore, FDA published this draft guidance on May 30, 2018 for public comments. Pharma or biotech companies that have concerns should provide comments back to FDA by December 15, 2018.

This ICH Q12 guideline is intended to complement the existing ICH Q8 to Q11 guidelines and includes a core guideline as well as annexes. It provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner. It is also intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions. Effective implementation of the tools and enablers described in this guideline should enhance industry's ability to manage many chemistry, manufacturing and controls changes effectively under the firm's pharmaceutical quality system with less need for extensive regulatory oversight prior to implementation. The extent of operational and regulatory flexibility is subject to product and process understanding (ICH Q8 and Q11), application of risk management principles (ICH Q9) and an effective pharmaceutical quality system (ICH Q10).

Flatter FDA Organization Proposed by FDA Commissioner Gottlieb

The FDA is proposing to reorganize the Office of the Commissioner to elevate the agency's medical product centers to report directly to Commissioner Scott Gottlieb. With the proposed relevelling of FDA's organizational structure by FDA Commissioner Gottlieb, the directors for the Centers for Biologics Evaluation and Research, Devices and Radiological Health, Food Safety and Applied Nutrition, Tobacco Products and Veterinary Medicine and for the Office of Regulatory Affairs would report directly to the FDA commissioner, eliminating an intermediate layer. This change would remove four intermediate offices that currently oversee the collective offices/centers under their jurisdiction: Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, and Operations.

NSF News...

NSF in India

In April 2018, Martin Lush, Global Vice President, Pharma Biotech and Medical Devices, was at the World Health Organization South-East Asia regional office, meeting senior leadership to discuss future training collaborations in India.

NSF IN THE COMMUNITY

Living NSF's Mission: Food Bank Volunteering

At the June 2018 global marketing meeting in Limerick, Ireland, the NSF team was proud to spend a day volunteering at the Mid West Simon Community food bank. A really fantastic organization helping the homeless and those at risk of homelessness, Midwest Simon supports people through their journey out of homelessness by providing appropriate accommodation and care services.

www.midwestsimon.ie

NSF Raises £4,000 for Local Charities

The NSF team in the UK recently raised £4,000 for two great local charities: Next Steps Mental Health Resource Centre, which helps local people with mental health problems, and Multiple Sclerosis Society Ryedale Branch, which provides emotional support, financial help and care services for those living with MS. Among other initiatives, a few of the NSF team completed a 22-mile charity coastal walk in North Yorkshire to help raise these vital funds.

Well done to everyone in the NSF team.

PROSYSTEM
an NSF International Company

Grand Opening of New State-Of-The-Art Training Facility in Hamburg, Germany

As a member of international standardization groups and based on our ongoing experience facilitating the development of important ISO and IEC standards for medical devices, we understand the requirements for regulatory education and training for employees of the health sciences industry.

This is why we designed a new state-of-the-art training center in the heart of Hamburg, Germany. The facility is outfitted with the latest AV conference equipment, is situated on the 20th floor and offers panoramic views of the city below. It is conveniently located and easily accessible by train, major throughways and airports.

Professionals working in the life sciences industry will enjoy courses in both German and English. See a sample of the course listings on the next page.

The facility and adjoining conference rooms are also available for rent.

Please join us at our open house and experience this wonderful new facility first hand.

Date: **December 5, 2018**

Time: **4pm – 10pm (CEST)**

Location: **Beim Strohhause 17, 20097 Hamburg, 20th floor**

RSVP: **JRockel@prosystem-nsf.com**

Forthcoming Courses & Workshops

What's Planned from November 2018 to March 2019

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

November 6, 2018 | Milan, Italy | Course Fee: €750 excl. VAT | AFI Discount €650.00

Medicinal Chemistry & Therapeutics

November 12 – 16, 2018 | York, UK | Course Fee: £3,500 excl. VAT

Pharmaceutical GMP

November 19 – 22, 2018 | Amsterdam, Netherlands | Course Fee: £2,370 excl. VAT

Pharmaceutical GMP Audits and Self-Inspections

A CQI and IRCA Certified Training GMP PQS Lead Auditor Course (Course no. 1773)

November 19 – 23, 2018 | Amsterdam, Netherlands | Course Fee: £2,970 excl. VAT

Data Integrity Workshop – *Presented in German*

December 4, 2018 | Hamburg, Germany | Course Fee: €830 excl. VAT

Pharmaceutical Packaging

January 14 – 17, 2019 | Hatfield, UK | Course Fee: £2,870 excl. VAT

Pharmaceutical Formulation and Processing Part 1

January 28 – February 1, 2019 | York, UK | Course Fee: £3,230 excl. VAT

Pharmaceutical Formulation and Processing Part 2

March 11 – 15, 2019 | York, UK | Course Fee: £3,230 excl. VAT

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

March 19, 2019 | Manchester, UK | Course Fee: £810 excl. VAT

Regulatory Affairs for QA: Marketing Authorisations

March 20, 2019 | Manchester, UK | Course Fee: £710 excl. VAT

Regulatory Affairs for QA: Variations

March 21, 2019 | Manchester, UK | Course Fee: £710 excl. VAT

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

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

March 21, 2019 | Amsterdam, Netherlands | Course Fee: £810 excl. VAT

Pharmaceutical GMP Audits and Self-Inspections

A CQI and IRCA Certified Training GMP PQS Lead Auditor Course (Course no. 1773)

March 25 – 29, 2019 | Manchester, UK | Course Fee: £3,040 excl. VAT

Pharmaceutical GMP – *Presented in German*

March 26 – 28, 2019 | Hamburg, Germany | Course Fee: €2550 excl. VAT

Events We Will Be Exhibiting and Speaking At in 2018:

PDA Europe Conference: Outsourcing and Supply Chain November 6 – 7 | Seville, Spain

Pharma Integrates November 12 – 13 | London, UK

ISPE UK Annual Conference November 22 | Old Windsor, UK

Food and Drug Law Institute Enforcement December 12 – 13 | Washington DC

Medical Device Regulatory Country-Specific eLearning courses

NSF International is the first organization to launch this eLearning training series, providing in-depth knowledge of the regulatory requirements of Australia, Brazil, Canada, Japan, and the United States (all MDSAP-participating countries), all structured in a consistent format to enhance the user experience.

Each course includes knowledge checks and final exams to test understanding and provide evidence of competency as required by ISO 13485:2016.

MDSAP Overview Training

A web-based course offering your organization the flexibility and efficiency of a virtual classroom to prepare for MDSAP. Presented by Kim Trautman, former US FDA official and key member of the original MDSAP development team, this course teaches the basics of the new non-conformance grading system and what grades trigger regulatory follow-up. You'll learn about the MDSAP audit model, audit time calculations, the information to be included in the audit report, and the MDSAP timeline.

This course includes a final exam and a certificate of successful completion, providing evidence of competency as required by ISO 13485:2016.

Find out more information on NSF's medical device eLearning:
nsfmedicaldevices.trainingfolks.com

Key to Symbols: Workshop | QP course | Presented in German

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.

Advanced Program in Pharmaceutical Quality Management

Presented in conjunction with the Indian Drug Manufacturers' Association, Series One of our Advanced Program in Pharmaceutical Quality Management (APPQM) has been successfully completed. Results and feedback have exceeded expectations.

INDIAN DRUG MANUFACTURERS' ASSOCIATION

Return on Investment for Attendees and Participating Companies

The 34 graduates (pictured) achieved remarkable results during this modular, MBA-style program:

> They **collectively generated $ millions in savings** for their parent companies by successfully applying the knowledge gained on the course to their workplaces. Under the guidance of course tutors, they completed projects on document simplification and reducing human error, OOS and deviation incidents, reducing WFI drain times, plant decontamination and streamlining validation processes.

> Attendees **dramatically improved their skills and expertise** in areas so vital to their company's future:

- **The art and science of brutal simplification** to drive out costs and improve compliance
- How to create a **high-trust, fail-fast culture**
- **Risk-based decision making** and **advanced risk management** to manage risks proactively
- **Advanced problem-solving** to fix root cause and drive continuous improvement
- **How to use data to drive continuous improvement**
- How to manage **change effectively**
- **Best business practices** from Google, Amazon and others

> Attendees **significantly improved their leadership and communication skills** by participating in some very challenging problem-solving and decision making scenarios. Their companies now have leaders for the future.

Why the APPQM is So Important to Your Patients and to Your Future?

India is the 'pharmacy of the world'. More than 80 percent of medicines supplied to patients in North America and the EU come from Indian companies. But the world is changing:

> The price of generic medicines continues to tumble. A cup of coffee is now more expensive than some lifesaving medicines. Unless companies can reduce costs without compromising compliance, they will not survive. Simplification is survival.

> Companies who succeed and prosper will be those who excel at:

- Creating a fail-fast culture where problems, errors and mistakes are used to drive continuous improvement
- Problem-solving
- Fast change management
- Risk-based, data-driven decision making
- Using their pharmaceutical quality system for competitive advantage

This is why the APPQM focuses on developing the knowledge, skills and competencies in these areas to Ph.D. level.

> *"Changed me as a person. Increased understanding of the pharma industry. Work-based project was an eye opener in terms of work culture change required and money that can be saved in the process."*
>
> **Ankit Chordia, Medopharm.**

> *"The topics covered in training all are essential in our business. It helped us to enhance capability and compliance."*
>
> **Tushar R Patil, Cipla.**

Registration for Series Two is Now Open: Remaining Places are Limited

Series Two starts on **November 19, 2018 in Bangalore, India**. Places are strictly limited, so please don't delay in booking.

To find out how much delegates loved the APPQM and see the course in action, visit the videos section of our resource library (**www.nsf.org/info/pblibrary**). Some delegates even said the APPQM was better than their MBA program. Find out why.

Dates for Series Two

Module One: **Pharmaceutical Quality Management Systems – Best Industry Practices**
November 19 – 22, 2018 | Tutors: Martin Lush and Lynne Byers

Module Two: **Managing Change; Change Control and Deviations**
January 21 – 25, 2019 | Tutors: Rachel Carmichael and Lynne Byers

Module Three: **Human Factors – Getting People to Follow the Rules**
February 25 – 28, 2019 | Tutors: Lynne Byers and Rob Hughes

Module Four: **Data Analysis for Business Improvement**
April 8 – 11, 2019 | Tutors: Pete Gough and David Young

Module Five: **Quality by Design, Process Validation and Technology Transfer**
May 27 – 31, 2019 | Tutors: Pete Gough and Bruce Davis

To register or for more information, please contact Martin Lush, NSF International's Global Vice President of Pharma Biotech and Medical Devices at **martinlush@nsf.org** or Mr SMM Mudda (Course Director) at **mudda.someshwar@gmail.com**. **If you would like this course customized to meet your exact needs, we can present the APPQM in house as well**.

NSF Case Study

How to Correct an Unexpectedly Difficult GMP Inspection and Prevent a Relapse

The Situation

The client received an FDA 483 report following an inspection of a European manufacturing facility with significant non-conformances identified, many associated with QC data trails and data integrity. A second site in the network experienced the same concerns during a subsequent FDA inspection. As an established CMO supplying global markets, the organization needed to respond quickly and thoroughly to avoid market action and loss of reputation.

The Methodology

Our team began a rapid process to determine the root causes of the non-conformances, understand the broader and site-based systems that had not predicted or addressed the issues before they came to light, and embark on a dialogue to engage the company's leaders and SMEs to accept the reality of the situation and engage in objective, science-based decision making. Being able to call out the issue and apply multiple perspectives in resolving and preventing recurrence was absolutely critical in helping to decide the best-fit actions.

The methodology followed NSF's BITE Toolkit and was designed to diagnose the issues; assess the risks to products, patients and the supply chain; and then apply carefully designed corporate and site-based changes.

The Execution

The priority was to assess the risks and identify any need for market withdrawal and recall. This involved first-hand review and assessment of QC data trails against the ALCOA expectations. Policies, SOPs and local routines were redesigned to ensure staff know when and where a data integrity risk exists and how to address it. NSF led a series of systems-based gap analyses, group and 1:1 coaching, and oversaw and verified CAPAs. A combination of audit, consultancy, coaching and education made sure that all changes were proportionate, sustainable, easily justified and targeted to prevent risk.

The Results

Thanks to the team approach, the site avoided a warning letter and could justify that no market withdrawal was necessary, preventing interruption of supply to a range of life-saving drugs. The client's reputation – in the eyes of the regulator and their client base – was actually enhanced by the speed, diligence, commitment and simplicity that characterized the changes made. The client was inspired by NSF to change the behaviors and mindset that led to the non-conformances, re-aligning priorities and resources to enhance the wider team and restoring confidence that they were structured to do the right thing for the short- and long-term.

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