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CHANGING REGULATIONS | Here to Support You Wherever You Are

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welcome

"Everyone has a plan until they get punched in the mouth". Mike Tyson

A few months ago, my son took a risk. He entered a university boxing match having never boxed before in his life. He trained hard and had a plan in place to win. He got knocked out in the third round. His opponent was faster and fitter than he had expected, and he didn't adjust his winning plan accordingly. In the world of pharma and medical devices, adaptability (changing plans fast) is now more important than productivity. This edition of the Journal focuses on helping you to roll with the punches and change plans quickly, so you don't need to use smelling salts.

Adaptability requires a well-educated and skilled workforce. ***How to Get More Training Budget in a World of Scarcity*** (page 3) is an essential read. Unless you fancy hitting the canvas.

Sometimes the knockout blow can come from your third parties. John's article ***Is Your Outsourcing Project Out of Mind and Out of Hand*** (page 7) provides vital instruction on how to stay upright from someone who has gone a few rounds.

Boxing rules may have remained the same for centuries but that's not the case in our industry. ***FDA's Sentinel Initiative*** (page 8) and the ***EU MDR*** (page 18) remind us of the need to understand the rules and change our plans before we get into the ring.

Sticking with the boxing metaphor, we're in your corner when you need us. We can be your coach in terms of not getting knocked out (prevention) or your paramedic during a global fist fight (lots of change and uncertainty). I hope you find this edition useful.

Just in case you were wondering, my son did make a full recovery and has no plans of returning to the ring. Both Mum and Dad are relieved. He has taken up ultramarathon running instead.

Martin Lush

Martin Lush,
Global Vice President, Pharmaceutical Services
and Medical Devices, NSF International

HOW TO GET MORE TRAINING BUDGET IN A WORLD OF SCARCITY

by Martin Lush, Global Vice President, Pharmaceutical Services and Medical Devices, NSF International

"If you think training is expensive, try ignorance."
David Begg

Let's start with a case study…

Back in 2016 I spent time with a company struggling on every front. Compliance was poor, productivity at an all-time low and products were coming off patent. They were facing a revenue cliff. Every dollar spent had to be justified and 35% savings made. Anxiety permeated the four-day budget meeting where departmental heads made their case for a slice of the ever-diminishing budget pie. Inevitably, there were winners and losers. Here's a quick précis of the meeting minutes:

- Manufacturing department's request for a new filling machine? Approved. Why? Because there was a quantifiable return on investment (ROI) as it could fill faster and better.
- Engineering's request for a new HVAC system? Approved. Why? The plant would be able to operate 24/7. Another ROI no brainer.
- QC lab's request for an automated self-injection system? Approved. Why? Reduced salary costs. Another qualifiable return on investment.
- Request for additional training in risk-based decision-making, root cause analysis and problem solving? Rejected. Why? No perceived ROI.

When there was a quantifiable benefit (ROI), money was available. No quantifiable ROI meant budgets were maintained or cut. I followed the head of training and development from the room. She was utterly dejected. For the third year in succession her training and education budget had been cut by between 7-11% each year.

> "***Martin, it's always the same. Because I can't link training to a quantifiable dollar value it's considered a cost rather than an investment. We only have money to cover the basic GMP refresher training to tick the compliance box... What am I doing wrong? Can you help?***"

I sat down with the chief financial officer to help him see the light. I kicked off with the adage:

CFO to CEO: "*What happens if we train all these people and they leave?*"

CEO in reply: "*What happens if we don't, and they stay?*"

He wasn't impressed, "*Martin, we've spent over £300K on training in the last 18 months and seen nothing back in return*".

I found out he was right. In addition:

- Training was rarely targeted to meet a specific business need.
- Most of the training program focused on the "how" (task specific), not the "why".
- Training effectiveness was not assessed, only short-term memory using questionnaires completed immediately after each training course.
- Most training was classroom, PowerPoint based. We all know that over 90% of information conveyed in this way is forgotten within 24-48 hours.

- No one understood that training alone changes nothing. As I have said in previous articles and YouTube videos (*Changing GMP Behaviors Part One and Part Two*), improvements in workplace behavior needed for that illusive ROI depend on:
  - Intrinsic motivation. People need a "What's in it for me?" and to understand the "why".
  - Those trained must be capable of applying the new knowledge by using simple processes, simple SOPs and simple tools.
- Training requires practice and learning from failure until the new behavior has become habituated.
- And finally:

Quantifiable return on investment had never been calculated.

However, this story has a happy ending. Over 12-18 months:

- The site's training budget increased, outpacing productivity gains. By 2018 they were spending more on training and education than ever before. Their training budget increased by an average of 34% each year in real terms.
- Productivity increased by 30%. They were making more quality product, faster. Rejects, repeat deviations, reworks and work in progress were all reduced.
- Compliance improved dramatically.
- Staff attrition fell from 18% to less than 5%. Why? When people feel cared for (invested in), they tend to stay and (usually) with a smile on their face.

So, how (in an environment of scarcity) can you get the same results?

How do you convince leadership to spend more on training and to keep critical programs at the top of the list of budget priorities?

YOUR SIX TO FIX TO INCREASE YOUR TRAINING BUDGET AND IMPROVE YOUR BUSINESS

1. Make sure every training program is linked to a specific business need, not just compliance, the more specific the better

One of the site's top three priorities to improve compliance and productivity was to reduce repeat deviations. They wanted to invest in a training program to "certify" those responsible for conducting the investigations. More later.

2. Identify what workplace behaviors must change to achieve this business need

Remember it's all about improving workplace behaviors and performance, not the knowledge transferred in the classroom. The site identified behaviors they wanted to change.

3. Calculate ROI before asking for the money

This is an essential step that is often missed and causes training proposals to get turned down. I sat down with the head of training and her colleagues in finance to justify the investment.

This is what was eventually presented to the senior leadership team for approval:

Business need – improve productivity and compliance: Reduce repeat deviations.

Training need: Investment in NSF's three-day deviation investigators certification program to reduce repeat deviations by 30% in 8 months.

Underpinning knowledge required for certified investigators:

- How to do the "gemba in 10," getting to the scene of the incident in under 10 minutes
- Products and processes (key quality attributes and critical control points)
- Risk-ranking tools and techniques
- How to investigate the error chain (remember there is no such thing as root cause)
- The vital soft skills needed for every investigation including:
  - Risk-based decision-making to allow risk-smart (not risk-averse) decisions
  - The Kline process (open-loop questioning)

- Six Thinking Hats
- Force field analysis
- Fishbone
- F – A – U (facts: assumptions: unknowns)
- B = M.A.t.H.

> How to move from CAPA to PACA and become more preventive focused

Working with their finance department we estimated that the labor and admin costs for each repeat deviation was approximately $12.5K. The actual costs would have been considerably higher if we had considered other factors such as delayed product release, extra rework and retraining. Given the high numbers of repeat incidents, a 30% reduction would provide more than $1.8M in savings.

Because there was such a strong case, the investment required for the course was approved. Making such a convincing business case is also a very strong motivator to deliver the results. If you don't, your credibility will be questioned next time around.

4. Make sure you adopt the 10/20/70 model to take training out of the classroom and into the workplace

This model has been mentioned many times in the past. 10/20/70 simply represents the amount of time in training spent conveying the essential why and what (10%), practicing the skills (20%) and application in the workplace (the 70%).

5. Establish a learning and feedback loop to see how things are improving (or not)

Behaviors (and improvements) don't change overnight. If you are not seeing improvements, find out why using our B = M.A.t.H. model

> Lack of intrinsic motivation?

> Overcomplexity?

> Absence of trigger events (reminders of what to do)?

> Not enough practice, coaching and feedback?

Remember, you promised a ROI, so you have to deliver. It takes time for new habits to become established. Be patient, mistakes will happen so be ready! If you are not seeing improvements find out why and fix it.

6. Publicize your success

As soon as you start to see positive results, publicize the results in a language that resonates in a world of scarcity.

In summary

> Make sure training is linked to a specific business need

> Identify the specific behaviors (improvements) in the workplace you want to change

> Calculate the ROI before you ask for the money
  - Become best friends with your colleagues in finance
  - Become more financially literate and make sure the sums add up, remember your credibility is on the line

> Adopt the 10/20/70 approach

> If you're not getting the results, find out why and fix it

> Publicize your success by using language key decision-makers understand
  - Reduced rework time = X dollars savings
  - Faster output/turnaround = Y dollars
  - Less work in progress = Z dollars

by John Johnson, Vice President, Pharmaceutical Services, NSF International

Is Your Outsourcing Project "Out of Mind and Out of Hand"

In the global market, outsourcing is no longer an option, it is an economic necessity. It can be a tremendous asset to integrate another firm's capability and expertise into your network; and conversely, it can add complexity, additional cost and unpredictable risk into the supply chain. So how do you know if it's a good idea or not?

Risk management across a global supply chain has never been a stronger factor in assuring economic success than it is now. Emerging pharma hubs are springing up across the world and this provides us with many more options on where to place our valuable assets. Global communications, the growth of pharma knowledge and the broadening of scientific knowledge in newer locations have all contributed to a wider and more complex set of options.

The process of outsourcing has always been well defined, yet surprisingly not always well managed. The following key steps define the process (yet how many of these are in place and under control in your organization?):

OUTSOURCE PARTNER SELECTION

- Identify potential outsourcing partners
- Questionnaires to help you identify them
- Site visits
- Initial systems-based GMP inspection
  - Due diligence assessments, including business continuity planning
- Quality technical agreement
- Pre-production detailed GMP inspection
- Pre-production technical reviews
- Including decision on person in plant and setting up a technical partnership

INITIAL MANUFACTURING BATCHES

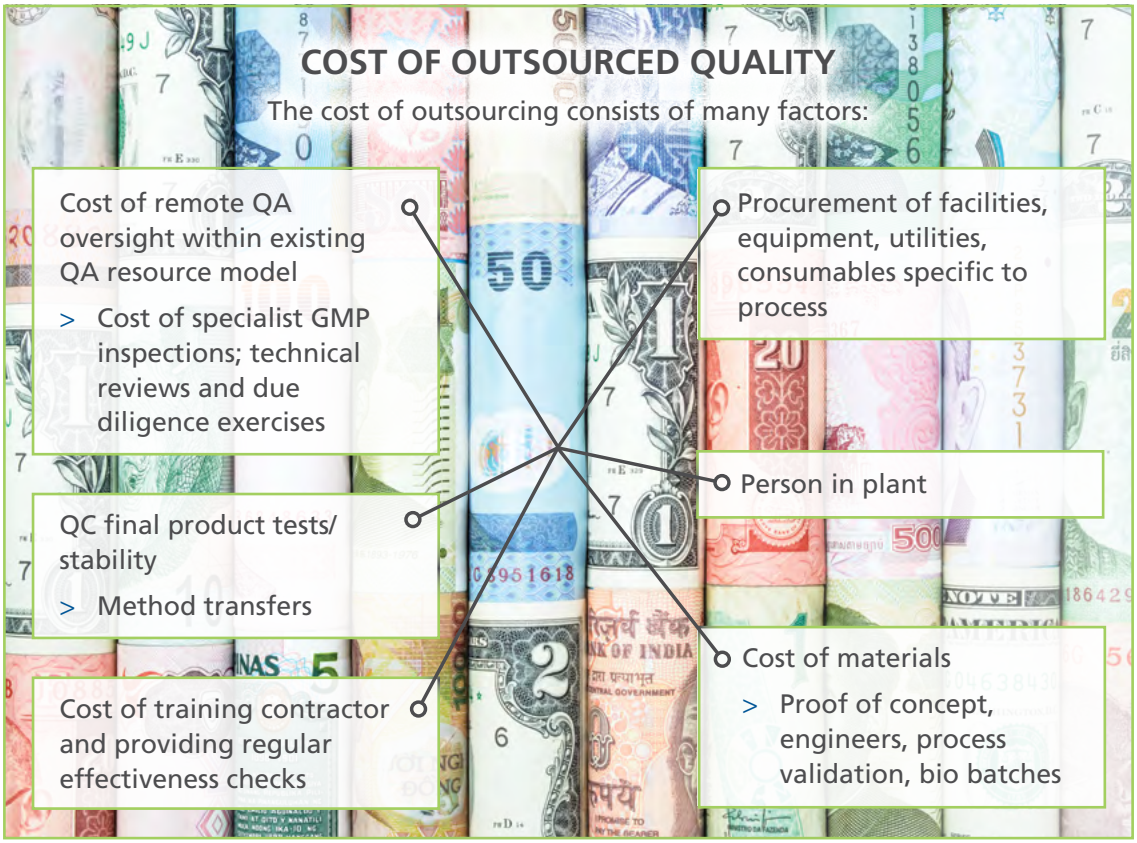
- Proof of concept batches
  - Can be small scale, but less risk at production scale
- Revision of quality technical agreement following technical and quality audits
- Engineering batches
- Process validation batches
  - Perform stability testing of outsourced material, e.g. Active Pharmaceutical Ingredient and final/or Drug Product (DP)
- Manufacturing of a bio batch
  - Includes stability testing of outsourced material and final DP
  - Can include some bioequivalence studies

Once the new contractor is established, a proportionate and insightful oversight program is needed and this will often include considerations for a person in plant, a management review process and technical/GMP on-site reviews.

NSF is noticing a trend where a variety of pharma companies want a third-party perspective on the suitability of an outsourcing option, seeking a thorough and impartial assessment of risk, distinctly outside of the influence of internal politics and financial targets. From such a review, NSF can measure the resource burden of setting up and providing ongoing monitoring of the outsourced location, the inherent risks and how to identify and manage them effectively. We can advise on any operational or GMP remediation programs needed to ensure the manufacturing location can provide a GMP compliant product "on time in full" and "right first time".

We have supported firms in finding contract laboratories and contract manufacturing organizations associated with sterile products, specialist biomaterials, non-steriles and APIs. We have performed due diligence assessments, business continuity plans and operational and quality reviews, allowing firms the 20:20 vision that is required to make the right decision for the right reasons.

See the information on priorities, costs and key messages when contracting out a manufacturing process.



KEY MESSAGES

- Keep a very close eye on your contractor – risk levels tend to change quickly!
- Key hazards include:
  - Initiative overload
  - New business
  - Staff turnover
  - Management changes
  - Regulatory expectations change without contractor's full attention
  - Contractor not turning out how you thought they would

CONTRACTING OUT – KEY LEARNINGS

The main takeaways from contracting out include:

- Outsource only for the right reasons and only to specialist proven contractors
- Use risk mitigation techniques in making the decision
- Work up a realistic budget for set-up and ongoing mentoring
- Be aware of and take action in the initial period
- Be detailed at management review
- Use specialist highly experienced GMP auditors and person in plant
- Ensure contractors are treated as an extension of your team and an integral part of your pharmaceutical quality system
- Select highly characterized products or low-risk dose forms to be carried out, e.g. formulation and fill/finish

NSF performs these types of assignments with a variety of firms across the world and can differentiate between good and bad decisions, and between solid and risky strategy. Allow us to help you avoid the heartburn of a risky sub-contractor. Contact us at **pharmamail@nsf.org**.

by Marinka Tellier, Director, Pharmaceutical Services, Regulatory Affairs, NSF International

FDA's Sentinel Initiative

Modernizing Pharmacovigilance

Pharmacovigilance (PV) is the continued assessment of the benefit-risk profile of new therapeutics that are approved for marketing by FDA and available for use in the real world. A therapeutic product's profile may differ from that observed in the clinical trials that supported the marketing approval, hence the regulatory requirement for postmarket surveillance.

The difference in profile can stem from several factors including exposure of a larger number of subjects that could reveal new adverse effects that occur at low frequency. In addition, exposure of the product to subjects with more variable medical backgrounds than specified under the inclusion/exclusion criteria of the pivotal clinical studies could result in a different benefit profile.

To date, PV has relied on active reporting to FDA by physicians and patients of adverse events including lack of effect (e.g. through FAERS) and required reporting by the product sponsor in the form of individual case reports, findings from medical literature and periodic postmarketing reporting (e.g. PSUR/PADER). A relatively newer tool that has supplemented FDA's PV surveillance has been the Sentinel System.

The Sentinel System was launched in 2008 following the 2007 FDA Amendment Act (FDAAA) which called for the creation of the postmarket Active Risk Identification and Analysis (ARIA) system to improve postmarketing surveillance. The Act required that FDA work with public, academic and private entities to develop a system to obtain information from existing electronic health care data from multiple sources to assess the safety of approved medical products.

This led to the creation of an electronic system by the Harvard Pilgrim Health Care Institute designated as the Sentinel Initiative. The system was initially piloted under the mini-sentinel study in 2009, with the full Sentinel System launching in 2016. The system focuses on drugs, vaccines and other biologics, and collects information from large amounts of electronic health care data (e.g. electronic health records, insurance claims data and patient registries) from a diverse group of data partners and academic partners. Importantly, it is the most comprehensive multisite, distributed database available to monitor the safety of marketed medical products in a manner that protects patient privacy and allows for real-time tracking (e.g. number of patients using a specific drug and side effects against medical history and use of other medications).

Five-Year Strategic Plan

The FDA is seeking to strengthen the use of the Sentinel System and issued its five-year strategic (2019-2023) plan to expand its use in January 2019.

The outlined strategy focuses on five areas. One is the continued enhancement of the system's infrastructure, technology and operations to support the capture and analysis of data. The second objective focuses on improving use of new advances in data science and signal detection. One example for this objective is the TreeScan project, which is intended to proactively scan for potential safety issues. TreeScan will simultaneously evaluate large numbers of potential adverse events or disease outcomes to determine if any occur with higher probability among patients exposed to a therapeutic product. Through this enhanced signal detection capability,

the Sentinel System can evaluate a product against the full spectrum of observed adverse outcomes as opposed to a pre-specified single adverse outcome. Eventually, when signal detection capabilities are fully developed, the system could examine all exposure variables across therapeutic products against all potential health outcomes simultaneously, and transform PV surveillance from a reactive to a continuous, real-time process.

The third strategic objective focuses on access and use of real-world data (RWD) and real-world evidence (RWE) generation. The Sentinel System will be used to establish standards for high-quality RWD and to evaluate RWE applications as part of FDA's catalyst program to advance the use of RWD in drug development and provide regulatory guidance in this area. In addition, the Sentinel System seeks to expand and validate new health outcome improvements (HOIs) relevant for the effectiveness of therapeutics to support adoption of RWD-sourced HOIs.

The remaining two strategic objectives focus on 1) expanding the stakeholders in the system to ensure its future as a national resource and its role in dissemination of knowledge and 2) using it to guide regulatory science, e.g. contribute evidence to support product label changes (see the Sentinel website for specific examples on how ARIA has been used).

Future Benefits

The Sentinel System is here to stay and seeking to play a more prominent role in PV by FDA and may be able to replace the manufacturer-driven PV activities in the future. Its potential to support use of RWD against validated HOIs in drug development and its ability to perform real-time monitoring of both safety and efficacy marks an important change in PV efficiency and effectiveness. It could contribute to shortened drug development time where in an ideal world it eventually may be capable of reducing the need for multiple Phase III trials to support marketing applications. Lastly, it can contribute to personalized medicine by being able to quickly evaluate efficacy in different patient groups, identifying those that benefit versus those that fail to benefit from new therapies.

For up-to-date information on the Sentinel Initiative and the full strategic report, see: **www.sentinelinitiative.org** ▶

and the FDA Sentinel Initiative section of the FDA website. ▶

If you have questions, contact us at **USpharma@nsf.org**.

Pharma Update

Regulatory Update

by Pete Gough, Executive Director, Pharmaceutical Services, NSF International

& Marinka Tellier, Director, Pharmaceutical Services, Regulatory Affairs, NSF International

Pharma EU News

New EU Veterinary Medicines Regulation 2019/6

The EU published a new Veterinary Medicines Regulation 2019/6 in January 2019 that will repeal the current Veterinary Medicines Directive 2001/82/EC. The new regulation will become applicable from January 28, 2022.

To reduce red tape, the new regulation includes:

- A centralized marketing authorisation process that will allow companies to place and maintain a veterinary medicine on the entire EU market
- Simplified pharmacovigilance rules
- New rules for veterinary field trials (clinical trials)

Article 97 of the new regulation contains the requirements for Qualified Persons and batch release, which are similar to the existing provisions in Directive 2001/82/EC but rather than "signing in a register," the QP is required to "draw up a control report".

EMA Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container

This guideline was published on March 9, 2019 by the European Medicines Agency (EMA) and will come into effect on October 1, 2019. It provides information on when alternative terminal sterilization processes, sterilizing filtration or aseptic processing could be accepted and what documentation is expected for sterile finished products, sterile active substances, sterile excipients and sterile primary containers in a new marketing authorisation application or a variation application for a medicinal product.

This guideline replaces the previous annexes to pharmaceutical development decision trees for the selection of sterilization methods (human and veterinary). It also revises the information on methods of sterilization previously described in the note for guidance on manufacture of the finished dosage form (human and veterinary).

EU-USA Mutual Recognition Agreement

The schedule for implementing the EU-USA mutual recognition of inspection agreement (MRA) continues to be met. The FDA has confirmed the capability of Poland, Slovenia, Bulgaria and Cyprus. This just leaves four Member States to be confirmed by July 15, 2019. The four remaining member states are Germany, Luxembourg, Slovakia and Netherlands.

EMA Marketing Authorisation Application Checklist

The EMA has launched a new marketing authorisation application (MAA) checklist that it hopes will make its validation process for MAAs more efficient by significantly reducing

the number of omissions applicants frequently make in their dossiers. The checklist has been launched as a five-month pilot and aims to increase the number of "first time right" submissions, which is currently only 10%.

The checklist includes questions that will help companies to assess the level of completion and consistency of the various sections in their applications. More information can be found in the updated pre-authorisation guidance questions and answers (Q&A) on the website. Applicants using the new checklist should submit it as part of their MAA dossiers.

Medical Devices EU News

MDCG Issue New EU Device Regulation Guidance

The European Medical Device Coordination Group (MDCG) is tasked to assist the European Commission with the harmonized implementation of the EU IVDR and MDR. In Q1 2019, it published three new guidance documents regarding the unique device identifier (UDI). The UDI will provide the traceability of devices required to improve postmarket vigilance by the competent authorities. The UDI will be assigned to all devices.

MDCG Finalizes Choice for Device Nomenclature

Following the release last year of a document outlining specifications for a medical device nomenclature, the MDCG announced in March that the Italian coding system (CND codes) has been chosen as the nomenclature system for Eudamed, the EU medical device database. To assist manufacturers, the CND codes will be mapped to Global Medical Device Nomenclature (GMDN), a device nomenclature used in several major jurisdictions including the U.S. The correspondence between the nomenclatures will be visible to operators and incorporated in the future database. This will allow all operators registering their device to find CND nomenclature equivalent to a GMDN code.

EMA and EU Device Regulation

The EMA has four new roles and responsibilities under the MDR and IVDR. These apply when a device incorporates a medicinal substance, for devices that are composed of substances systemically absorbed by the body to achieve their intended purpose, for companion diagnostics and in certain borderline cases involving medicinal products. EMA has published the first of a set of questions and answers relating to these areas, around the topic of Article 117.

One Notified Body Designated to the EU Regulation of Medical Devices

Q1 2019 also saw the first designation of a notified body for the MDR, BSI UK. With Brexit looming, it is hoped that BSI Netherlands also attains this status soon. We expect to see further notifications in Q2. Time is critical, given that there is only a year to the end of the MDR transition.

Brexit

The EMA has completed its relocation to Amsterdam, leaving the London HQ on March 1 and started to move into their temporary home in the Spark building on March 11, 2019. All EMA meetings are taking place at the Spark building (Orlyplein 24, 1043 DP Amsterdam, Netherlands) until the permanent building is finished.

The official address of EMA is now that of their permanent building: European Medicines Agency, Domenico Scarlattilaan 6, 1083 HS Amsterdam, Netherlands.

Medical Devices Update

by Laurence Matheron, Director, Regulatory Team, IVDs and Medical Devices, NSF International

& Robyn Meurant, Executive Director, Regulatory Team, IVDs and Medical Devices, NSF International

Regulatory
Update

Pharma US News

Despite the partial U.S. government shutdown that affected the FDA at the start of the year, a number of initiatives took place.

Orange Book – Ensuring Accurate Reflection of Marketing Status

In January, FDA issued a draft guidance on marketing status notifications to ensure that the Orange Book is up-to-date. The Orange Book contains various drug product lists: the so-called active sections, comprised of the Prescription Drug Product List and the Over-the-Counter (OTC) Drug Product List, and the so-called discontinued section that contains the Discontinued Drug Product List. The latter reflects drug products that have been identified by the NDA/ANDA holder as not being marketed or whose marketing has been discontinued for reasons other than safety or effectiveness, as determined by FDA. FDA relies on NDA/ANDA holders to timely notify the Agency of changes in marketing status as required by the regulations. The new guidance provides clarification on the definition of "not being marketed," reporting timelines and content of these type of notifications.

Drug Quality – Proposal for Development of Voluntary Consensus Standards

A new draft guidance, entitled CDER's Program for the Recognition of Voluntary Consensus Standards Related to Pharmaceutical Quality, issued in February aims to enhance product quality and expedite pharmaceutical development. The guidance proposes a program in which stakeholders and FDA staff have the opportunity to propose pharmaceutical quality standards for potential recognition by the FDA, providing industry with additional options for pharmaceutical development and manufacturing. Recognized standards would be listed on the FDA website as part of Agency transparency.

Manufacturing Innovation – New Draft Guidance on Continuous Manufacturing

FDA issued a new draft guidance to promote the uptake of continuous manufacturing (CM) as a replacement for traditional batch-to-batch manufacture. Adaptation of CM by companies has been limited to date with only a few marketed products being produced by CM. The new guidance provides more clarity about FDA expectations to aid manufacturers interested in transitioning to CM. It should be noted that CM is also being worked on by an ICH expert working group and will eventually be ICH Q13.

Innovation in Clinical Trial Design and Oversight

FDA issued a number of guidances aimed at modernizing clinical trial infrastructure where there has been reluctance in use of new approaches by sponsors and CROs. One example is a new guidance with strategies on how to incorporate patients with more challenging health conditions into oncology trials to make the trials more representative of real-world oncology. Another example is a Q&A draft guidance on risk-based monitoring that promotes incorporation of more computerized systems for effective clinical trial oversight

FDA Commissioner Scott Gottlieb Resigns

FDA Commissioner Scott Gottlieb, M.D. resigned in March 2019. Ned Sharpless, M.D., Director of the U.S. National Cancer Institute, will serve as Acting FDA Commissioner.

AVOID THE COST OF NON-COMPLIANCE
GIVE YOUR BUSINESS THE EDGE!

by Lynne Byers, Executive Director, Pharmaceutical Services, NSF International

The MHRA recently published a blog about the cost of non-compliance (It pays to be compliant!). The thrust of the blog was that the MHRA planned to charge companies for the time spent reviewing responses to the Inspection Action Group.

At NSF we are often called in to help companies respond to a regulator whether it is during the response process or to help with remediation. We are always happy to help, but we prefer to engage in a proactive manner. Forward-thinking companies approach us when they want to enter new markets or need help with self-identified deficiencies in existing quality systems.

Currently, we are receiving several requests for help with quality risk management (QRM) and data integrity (DI). These are not new topics and most companies have trained people in the theory of ICH Q9 and DI's ALCOA (attributable-legible-contemporaneous-original-accurate) principles. However, understanding the theory is one thing, but many people struggle with what it means in practice. We use Gemba in our in-house courses to open eyes to problems which are present but not seen. Both of these are hot topics for regulatory authorities, so I recommend you check whether QRM and DI are operating effectively in your organization. We are also running a Quality Risk Management workshop on the 24 September in Manchester, UK.

Companies who are proactive continuously ask themselves the following questions:

- How does my PQS compare to cGMP expectations?
- How should I manage a regulatory inspection?
- How can I reduce complexity and set clear, unambiguous standards?
- How can I ensure our behaviors assure company performance for the long term?
- How do I install education rather than training?
- How do I set standards for education and delivery?

Our EDGE toolkit can help improve GMP and business performance. We will work with you to find answers to these questions and implement the right measures through:

- GMP scorecards and self-assessment tools
- GMP regulatory inspection management
- Simplification and human error reduction processes
- Behavior and mindset change for long term success
- Education route maps, not training
- Staff certification programs

Our toolkit defines
Evaluation
Diagnosis
Guidance & checks
Effectiveness

See the brochure enclosed with this edition of the Journal for more information. If you have questions about our EDGE toolkit, please contact **edge@nsf.org**.

by John Johnson, Vice President, Pharmaceutical Services, NSF International

& Robyn Meurant, Executive Director, Regulatory Team, IVDs and Medical Devices, NSF International

Something Special is Happening in Ireland

Despite a decade of an economy that at times felt like a rollercoaster, the pharmaceutical and medical technology industry in Ireland continues to grow strongly. A multitude of factors has contributed to this rapid evolution, and the country can look back with some satisfaction in terms of harnessing a variety of committed and energetic government agencies that are active in promoting life sciences alongside the development of a stable, highly educated workforce.

The numbers speak for themselves (see *figure 1*).

NSF Involvement

NSF is proud to have played a part in that growth with:

- Assignments concerning facility design, qualification and operational support for both sterile and non-sterile production units.
- Audits, remediation plans and extensive internal training activities in Ireland and Northern Ireland.
- Over 75 delegates from Ireland pharma companies attending our public training courses in Manchester, York and Amsterdam.

In 2019, we plan to extend the range of services that are easily accessible to the Irish pharma and med tech sector so that:

- We run more internal training and education programs on-site as internal, customized events.
- We have a factory-based course, *GMP for Biological and Biotechnology Products,* allowing more hands-on, practical interpretation of GMP at the shop floor and management levels (visit **www.nsf.org/info/pharma-training**) as announced in the last Journal. John Johnson and Roger Guest are the expert tutors for this course at NIBRT (Dublin) 17-20 September 2019.
- We are expanding our local expertise and network to keep closer to the areas of innovation and investment.
- We are available to offer expert advice on meeting the demanding new requirements and impending timelines of the new EU regulation for medical devices and IVDs.

Looking Ahead

Some key features characterize this sector and we aim to combine our medical devices and pharma expertise to meet the challenges ahead, e.g.:

- More user-friendly (and often more complex) drug delivery systems.
- More combination products.
- An expansion in biosimilars as well as biologically active materials for some of the world's most challenging illnesses.
- A younger workforce that demands a different level of engagement and inspiration; not least that the learning and deployment style appears a step change away from those of us who joined the industry in the 1980s and 1990s.

Howard Broadbridge (Practice Manager, Medical Devices), Robyn Meurant (Executive Director, Medical Devices) and John Johnson (Vice President, Pharmaceutical Services) have been working closely with some existing and potential clients, government agencies and universities to study the conditions that have led to such a surging growth, alongside a growing reputation for GMP compliance, in Ireland. They are studying the success factors and holding them up against the challenges ahead, such as:

- How can this growth be sustained?
- Where will the industry leaders be created and how?

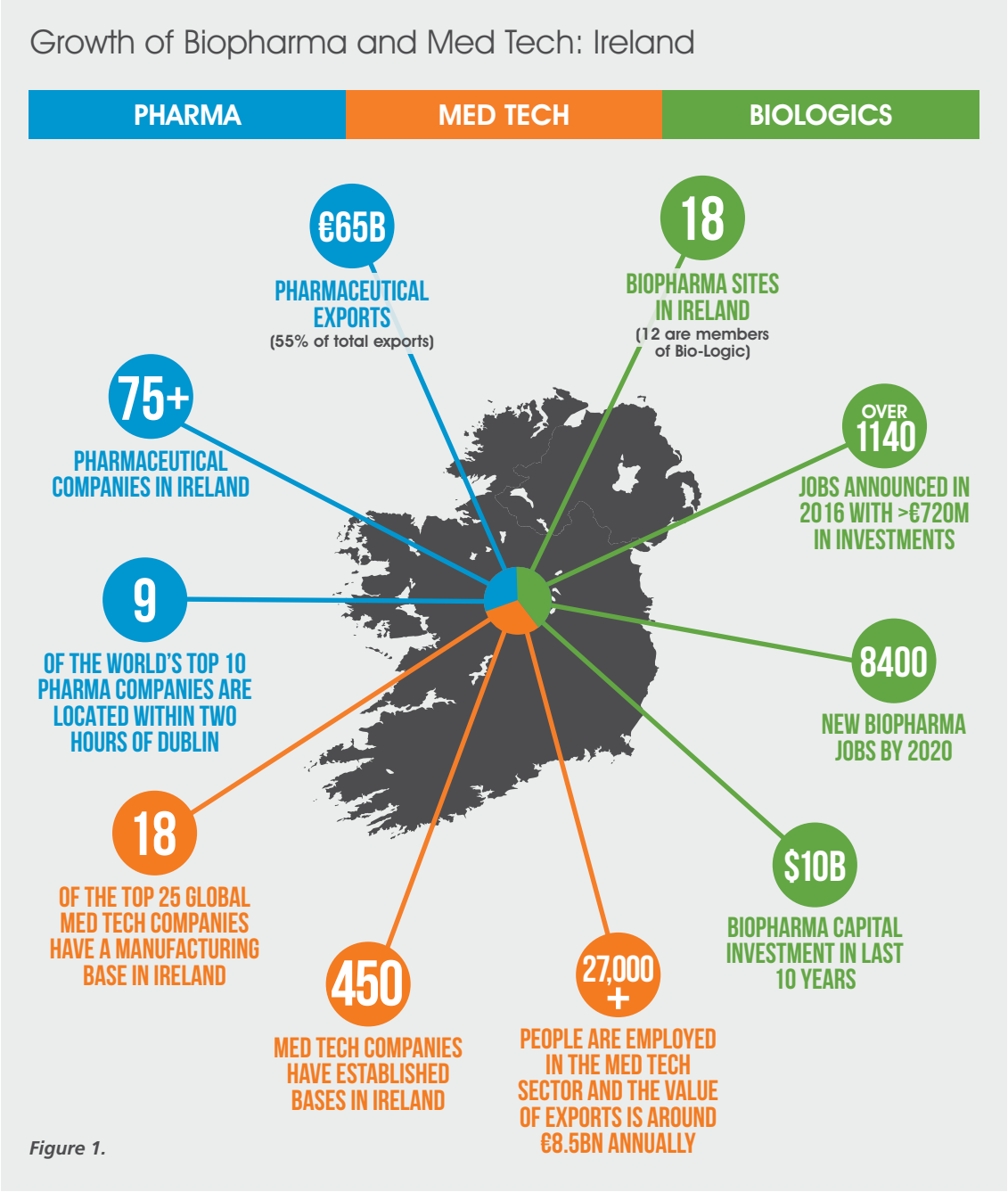


Figure 1.

- Where will all these new employees come from and how can they be inspired to engage with such a highly regulated industry to achieve perpetual GMP compliance as well as promote innovation?
- How will the startups and new facility builds move from construction or development to commercial facilities; what skills will they need?
- How will the Irish facilities compete in the global market perhaps utilizing razor sharp quality risk management, management of quality costs and refinement/ maturation of the quality system?
- How ready are Irish manufacturers for the EU MDR and the IVDR?

It is an exciting time for us at NSF, combining locations and competencies across pharma and med tech, leveraging our expertise and experience so that we support our clients' expansion plans. In the coming Journals, we will share some case studies of our work in this field, helping you to see how you might take your operation to the next level.

Associate Spotlights

by Sam Richardson, Marketing Specialist, Pharmaceutical Services, NSF International

Sam Richardson caught up with two of our pharma associates when they were in the York, UK area for the 2019 associate team meeting in February.

Meet James Culyer

So, tell me about your working background before joining NSF.

Over 20 years ago, I started working for a large-volume sterile parenteral manufacturer, Baxter Healthcare. I worked in the quality control (QC) laboratory as an analyst for just over five years before moving into the quality engineering/validation team.

From there I moved to Napp Pharmaceuticals, producing tablets, capsules and other solid doses and worked in the validation group for five years. I started my QP training with NSF in 2008 and qualified in 2010. By that time, I was working in supply chain assurance, which I continued for seven years, with roles leading up to global supply chain assurance. Before leaving the UK for South Africa at the end of 2016, I moved into the role of head of research, QA (pharmacovigilance, GCP, QA and clinical IMP QA).

Do you have a career highlight or highlights?

Tough question! A couple of project launches I was involved in were particularly rewarding, including some big product development activities. And, a couple of green field projects I got involved with were particularly interesting. Both involved working at sites outside of the UK: one in Cyprus and one in Israel. Dealing with the different requirements, cultures, facilities and expectations was fantastic and hugely satisfying.

So, when did you join NSF? And what made you want to work for NSF?

I joined in early 2018. NSF has a strong reputation. The perception of NSF is that it's an elite group with the highest levels of expertise and knowledge which is highly respected. To be part of that group is a great honor. A lot of the work I have done with NSF so far is mainly international, including work in Canada, China and India.

What would you say are your main areas of expertise in helping clients?

My main areas would be supply chain management, process and quality systems development, risk management as well as the fundamentals including auditing, coaching and GMP training.

A random one for you: What do you think are the most interesting challenges facing the pharma industry now and in the future?

I think it's going to be the global move towards harmonization and the global complexity of supply chains and, with this, the expectation on developing countries to meet international regulations, supporting export and import activities. They have to work toward a much higher level of compliance, which means increased costs and increased resources. If you balance that against the fact that health authorities are trying to drive down the cost of pharmaceutical products, it's a big challenge for companies.

On a lighter note, what are your interests and hobbies outside of work?

Sheila and I both volunteer at a Cheetah Conservation Program called Cheetah Outreach. It's great working with the animals. I love to go on safari trips and I'm also keen on trail running and mountain climbing. I'm currently training to do the Two Oceans Marathon, which is a big goal of mine for 2019 and will be a huge accomplishment if I manage to do it!

Good luck in the event! You will have to let us know how you get on.

Meet Sheila Shadbolt

So, what is your working background?

I was born and grew up in South Africa where I completed my initial university education (BSc in molecular biology and an MSc in chemistry). I then moved to the UK and worked in the pharmaceutical industry for around 17 years. I'm originally a chemist who's mainly worked in API manufacture and biological products manufacture, including sterile and aseptic manufacture work. I started out in quality control before various roles in quality assurance, validation and regulatory. My last role in industry was head of quality operations at a vaccine manufacturing site in the UK. I'm also a QP and joined NSF as an associate in 2018.

What made you want to work with NSF?

What made me want to work with NSF is its global reputation. I did of course do my QP training with NSF before moving back to South Africa in late 2016, so I'm very familiar with the people and the courses you run.

What made you want to move back to South Africa?

It's my home, so it was more for me due to family. I do a lot of work in South Africa as well as internationally. Most of the work I have done with NSF so far has been international.

Out of interest, who were the people you knew from NSF? Has much changed since you first met NSF's pharma team?

I knew Mike Halliday and Pete Gough very well, among others. There have been some changes, but the people and overall positive perceptions remain the same.

To put you on the spot, what would be your greatest work strengths in terms of where you can help clients?

I have a lot of experience with regulatory inspections, whether it's inspection preparation, remediation or even responding to inspections observations. That's definitely an area I can help clients, along with quality systems management and auditing in my specialist dosage form areas.

A random one now: What advice would you give to anyone starting their career in the pharma industry?

There are a lot of scopes and roles in the industry. Find your niche. There are so many different experiences you can have – some good, some bad. So carry on until you find the area that interests you, that you enjoy the most and that gives you the most job satisfaction.

I think there's a lesson we can all learn from that! Just one more question: What are your interests/hobbies outside of work?

I enjoy travel and particularly enjoy going to places that are culturally quite different such as African countries and the Far East. For instance, in South Africa now, we do quite a lot of 4x4ing, going to off-the beaten-track places. I enjoy outdoor pursuits like skiing and scuba diving.

We both volunteer at a Cheetah Conservation Program called Cheetah Outreach and get to work hands-on with a variety of African animals including cheetahs which is something quite special and unique to South Africa.

It was great to meet James and Sheila and have them on board. You can find their full bios on NSF's pharma website. If you have a question, don't hesitate to contact our team at pharmamail@nsf.org.

by Kim Trautman, Executive Vice President, Medical Devices, NSF International

EU MDR: What Does It Mean for the Medical Device Industry?

The new EU MDR raises a lot of uncertainty and concerns for manufacturers. **Kim Trautman**, Executive Vice President, NSF International, talks about the challenges for the industry and how these can be addressed.

WHAT ARE THE KEY CHANGES OCCURRING WITH THE EU MDR?

Kim Trautman: Firstly, manufacturers are no longer allowed to use data published in the scientific literature pertaining to competitors' products in the same way to state that their product is equivalent. They must have the specifications for that other device, which is highly improbable unless it is part of the same company. There will likely be some new clinical investigations or evaluations, depending on the risk.

Another big change is the risk management and usability engineering throughout the lifecycle of the device. There's a standard in the risk management community that you can take action as far as is reasonably practical. The EU MDR talks about taking it as far as possible. While this may seem like semantics, it's really not.

There are also a lot of different requirements for labeling, including the unique device identification (UDI). Beyond the UDI, there are additional demands for risk management, where if risks cannot be reduced to as low as possible, they might have to go on the label or in the instructions for use.

ARE THERE ADDITIONAL POSTMARKET SURVEILLANCE AND OTHER PREMARKET REQUIREMENTS?

Yes, postmarket requirements go beyond typical complaint-handling. There are more specific requirements such as postmarket clinical follow-up, whether that be in clinical evaluation reports for regular devices or performance evaluation reports for in vitro diagnostic devices, under the EU IVDR. And then there are new roles and responsibilities for economic operators within the premarket arena, such as the authorised representative, legal manufacturer, importer or distributor.

Every single one of these changes will indirectly or directly affect the quality management system. To meet these new requirements, manufacturers must break down the silos that traditionally exist between regulatory affairs and quality assurance.

WHAT ARE THE TIME FRAMES FOR THE EU MDR AND HOW CAN MANUFACTURERS PREPARE?

The main deadline for the EU MDR is May 2020. Manufacturers are allowed to maintain their current certifications until they expire. However, if a manufacturer makes a "significant change" after May 2020, it has to switch to the

new regulation and be prepared for those changes. While the deadline for the IVD Regulation is May 2022, IVD manufacturers must also be prepared.

Preparations typically start with a gap analysis, comparing the current processes and procedures with what the regulation requires. From there, they need to march through a very methodical, project-managed timeline to start handling some of those gaps. Companies have to decide whether they are going to hire additional resources to keep it in-house or if they will be going outside to third parties for some of these functions. Ultimately, a manufacturer's QMS must be able to sustain these changes and remain compliant with the requirements of ISO 13485:2016.

HOW DOES NSF HELP SUPPORT COMPANIES TO IMPLEMENT THESE PROCEDURES?

One of my big roles at NSF is training. We are continually producing eLearning resources and face-to-face training because regulations are constantly changing. If people haven't thought of some of these things, there is a fantastic eLearning module on the new regulation (visit **www.nsf.org/info/md-training**). We also have several experts that are ex-regulators who worked in the EU and can provide many different consulting services.

NSF goes beyond traditional consulting. We have people involved in clinical evaluation reports, tech file remediation and performance evaluation reports. They are now helping companies remediate those files and keep them updated. A call to action is the biggest message.

Companies cannot wait for more guidance – they need to act now.

If you have questions or need assistance, contact our team at **medicaldevices@nsf.org.**

What's New at NSF?

New Training Center in Hamburg

PROSYSTEM, an NSF International company, has opened a training facility in Hamburg, Germany. Located in the Berliner Tor Center, the new location expands its services to the European Union's medical device and pharmaceutical manufacturing industries.

Oliver Christ, Executive VP of PROSYSTEM said, *"NSF's new training center in Germany expands our regulatory training and education programs to better support medical device and pharmaceutical manufacturers competing in the fast-changing European marketplace".*

The expansion doubles the existing office space with an additional floor in the Berliner Tor Center, one of Hamburg's tallest office buildings.

To celebrate, NSF held an official grand opening event on December 5, 2018. Experts from NSF and industry attended the event which included presentations on the story of NSF, healthcare 2025 (the future of the pharma and medical device industries) and advantages of face-to-face training.

Led by Christof Langer and Catherine Kay, NSF also hosted a complimentary two-day Human Error Prevention course, presented in German on December 5 and 6, 2018 which was well attended by over 25 pharma and medical device professionals and received great feedback.

For current course listings in Hamburg, visit the PROSYSTEM website, **www.prosystem-ag.com/en** and **www.nsf.org/info/pharma-training.**

L to R: Heather Taylor, Oliver Christ and Kim Trautman

NSF News...

NSF in India – Someshwar M. Mudda Joins the Team

To further expand NSF's capabilities in India, Mr. Someshwar M. Mudda has joined NSF as President of Pharmaceutical services supporting training and consultancy activities in the Asia Pacific region. Mr. Mudda is a trusted specialist with over 40 years' experience in pharmaceutical manufacturing. He has designed world-class, GMP-compliant facilities of various dosage forms for plants that have been approved by the agencies such as the UK MHRA, U.S. FDA, WHO, MCC, South African Health Products Regulatory Authority, Health Canada and ANVISA Brazil.

His areas of expertise include:

- Technical and strategic leadership for design and operation of plants consistent with global standards for operations, quality and compliance
- Close connections with the national and global thought leaders in the areas of pharmaceutical quality management and cGMP regulation
- Design and implementation of best-in-class pharmaceutical quality systems for consistent implementation of GMPs harmonized with the global requirements

Mr. Mudda also serves as a technical advisor and leadership mentor to many leading Indian companies and is the Chairman of the Regulatory Affairs Committee of the Indian Drug Manufacturers' Association (IDMA).

He is also the program director of NSF's *Advanced Program in Pharmaceutical Quality Management*, offered in collaboration with IDMA for the senior executives of the industry. This unique, internationally recognized and independently assessed program is specifically designed for Indian companies who want to succeed in U.S. and European markets, providing individuals and companies with what they need to succeed.

NSF IN THE COMMUNITY

NSF Raises £4,436 for Local Charities

The NSF team in the UK raised £4,436 throughout 2018 for two great local charities. Ryedale Foodbank, which aims to make sure that no one in the local community goes hungry by providing emergency food and support to local people in crisis, and Carecent, which is a breakfast center for all homeless, unemployed or otherwise socially excluded members of the community. Among other initiatives, the NSF team put on a Christmas raffle, made fresh cakes and held cake stalls at the local market, and hosted a Body Shop party to help raise these vital funds.

Well done to everyone in the NSF team.

Ryedale Foodbank

Carecent

Team Hosts Inaugural Training Course in Ann Arbor

In February 2019, we ran our inaugural CQI and IRCA Certified GMP PQS Lead Auditor Training course at the NSF Headquarters in Ann Arbor, Michigan, U.S.

Executive Vice President Mike Halliday said, *"This course took place because QA leaders from two companies each wanted teams trained through our CQI and IRCA Certified GMP PQS Lead Auditor Training course. Both had trained many in-house before and this course meant they could be efficient on tutor and venue costs. Despite snow and -14˚C temperatures, the course was a huge success and delegates flew in from Europe, Asia and across the Americas to work together to improve and fine-tune their auditing skills. It was a great group and a great pleasure to work with as a trainer, along with my fellow trainer Darren Jones".*

NSF's Pharma Team Awarded findcourses.co.uk Customer Outreach Award

NSF International's pharma team has been awarded findcourses.co.uk's 2019 Customer Outreach Award, surpassing over 200 companies in training enquiry response times.

The Customer Outreach Award is only given to trusted training providers who meet customer expectations. According to findcourses.co.uk's most recent training buyer's report, 39% of training buyers expect to be contacted in under 60 minutes when they put through a new enquiry. In 2017, findcourses.co.uk reports that only 17% of training companies met that standard.

"It's exceptionally important for training providers to respond to customers in a fast and effective way," says findcourses.co.uk Site Manager, Sophie Austin. *"In today's hyper-connected world, expectations often grow faster than companies can respond. With the rapid expansion of corporate social media and the opportunity to instant message companies, response time expectations are only set to get shorter, and it's vital that companies are able to respond quickly without compromising on the quality of their reply. That's why we do not include automated responses in our measurements – we require replies to be thoughtful, considered, but most of all – helpful.*

We are particularly proud of our trusted partners, such as NSF International, as we know they will consistently offer training buyers a high standard of customer service."

Forthcoming Courses

What's Planned From July to September 2019

Pharmaceutical GMP Audits and Self-Inspections
(A CQI and IRCA Certified Training GMP PQS Lead Auditor Course)
July 1 – 5 | Oxford, UK | Course Fee: £3,040

Quality Management Systems Lead Auditor Training Incorporating ISO 13485:2016 and MDSAP Requirements
(CQI and IRCA Certified Medical Devices Training)
July 8 – 12 | Washington, D.C., U.S. | Course Fee $2,700

The Role and Professional Duties of the Qualified Person
July 15 – 18 | Brighton, UK | Course Fee: £2,870

Mathematics and Statistics
September 9 – 12 | York, UK | Course Fee: £2,870

Statistical Process Control
September 9 – 10 | York, UK | Course Fee: £1,420

Statistical Testing
September 11 | York, UK | Course Fee: £710

Deviation and CAPA Management
September 10 | Stansted, UK | Course Fee: £710

Human Error Prevention
September 11 – 12 | Stansted, UK | Course Fee: £1,420

Pharmaceutical GMP Audits and Self-Inspections
(A CQI and IRCA Certified Training GMP PQS Lead Auditor Course)
September 16 – 20 | York, UK | Course Fee: £3,040

GMP for Biological and Biotechnology Products
September 17 – 20 | Dublin, Ireland | Course Fee: €3,400

New Annex 1: How to Develop an Effective Contamination Control Strategy
September 17 | Milan, Italy | Course Fee: AFI member: €665, Non-AFI member: €770

A-Z of Sterile Products Manufacture
September 23 – 27 | Hamburg, Germany | Course Fee: €3,825

Quality Risk Management
September 24 | Manchester, UK | Course Fee: £710

Supplier Management
September 25 – 26 | Manchester, UK | Course Fee: £1,420

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

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

MEET OUR PHARMA AND MEDICAL DEVICE TEAMS AT... AUGUST TO NOVEMBER 2019

- **International Summer School: Discovery and Development of Diagnostics for the Early Detection of Cancer** | July 15 – 18 | Cambridge, UK
- **24th Annual GMP by the Sea** | August 12 – 14 | Cambridge, MD, U.S.
- **AdvaMed Annual Conference** | September 23 – 25 | Boston, MA, U.S.
- **PROSYSTEM Symposium: Celebrating 75 Years of NSF, 20 years of PROSYSTEM**
  September 12 – 13 | Hamburg, Germany – Presented in German
  October 1 – 2 | Hamburg, Germany – Presented in English
- **RAPS Regulatory Convergence** | September 21 – 24 | Philadelphia, PA, U.S.
- **MedConf** | October 22 – 24 | Munich, Germany
- **CPhI Worldwide** | November 5 – 7 | Frankfurt, Germany

Complimentary Webinars: July to December

JULY	> Managing Contract Qualified Persons – What Do You Need from Them, What Do They Need from You?
	> Introduction to the GMP Standard for OTC Drug Manufacture NSF/ANSI 455-4 – 2018
SEPTEMBER	> What do Regulators Check for When Auditing Cleaning and Cleaning Validation
OCTOBER	> The UK Qualified Person – Best Practice for Gaining Eligibility
NOVEMBER	> What are the Key Topics When Auditing a High-Speed Packaging Facility
DECEMBER	> How to Resolve Conflict Within Multi-National Organizations so That Everyone Flourishes

Places are limited. Register online, **www.nsf.org/info/pharma-webinars**

NEW UPDATES TO OUR NSF PHARMA APP

You can now access training information and book courses while on the go! Download today, it's available on Apple's App Store and Android's Google Play.

Pharma and Medical Devices eLearning

Our pharma eLearning includes courses on SOP writing, the roles and responsibilities of a responsible person and much more. Our medical devices eLearning includes new courses on the EU MDR and the IVDR. Visit our website to see our range of eLearning.

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.

OUR PEOPLE DEFINE OUR ORGANIZATION. JOIN OUR PHARMA ASSOCIATE TEAM!

If you are an experienced industry professional, have a passion for making a difference and want to work for a reputable organization, then becoming an NSF pharma associate could be the role for you. Offering flexibility, we are looking to add some talented people to our European associate team and Lynne Byers would be glad to explain our vision and needs.

What we are looking for:

> Bilingual associates who can run training courses, consult and audit in two European languages, including English

> Individuals with over 20 years in pharmaceutical operations

> In particular, microbiologists, engineers and those with biotech experience

Our clients rate our associates as outstanding because:

> They are seasoned professionals who have walked in the client's shoes

> They quickly assess problems, engage with colleagues and create sustainable solutions to multifaceted issues with empathy, diplomacy and action-centered leadership

> They are recognized as industry experts in their field

Does this sound like you?

If it does, please get in touch with Lynne at pharmamail@nsf.org or +44 (0)1751 432 999.

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