Journal

ARE YOU
INSPECTION
READY?

75 YEARS
1944-2019

NSF

welcome

So, Why Do You Get Out of Bed in the Morning?

It's a well-known fact that everyone needs a WHY, a reason for caring and for getting out of bed in the morning. Virtually everyone I meet in our industry started their career with the same WHY – a passionate commitment to help others; to research, develop, manufacture and supply medicines and medical devices to keep people alive and well.

Before writing this, I went into our local pharmacy to collect my daughter's EpiPens since her old ones had expired. As many of you know, she has multiple allergies of anaphylactic (life-threatening) magnitude. In fact, her pens have been live savers on four occasions. The pharmacist returned with the prescription but no pens.

"Sorry Martin, there are no EpiPens available anywhere. She will have to use the expired ones."

He then showed me a list of 25 medicines, all unavailable. Not just in short supply but completely unavailable. His expression said it all.

"Why can't your industry do its job?"

Has over-complexity diluted our WHY? Are regulatory inspectors finding the same things repeatedly? Are over-complicated, even outdated, laws and regulations part of the problem? Find all the answers and much more in this edition.

As you read through, please keep asking yourself these questions:

> Do you still have your WHY?

> What are you doing each day to ensure the supply of safe and effective medicines?

For any of you struggling, *Words of Wisdom* from Anders Vinther (*page 9*) is a must read!

My pharmacy experience was a timely reminder that decisions made, and actions taken, have consequences. So, one last question:

What has our industry done to create some of the worst drug shortages in decades? If we can understand the WHAT and focus on the WHY, we can fix it.

Please let me know what you think (**martinlush@nsf.org**).

Martin Lush

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

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DOCUMENTATION COMPLEXITY
– At Crisis Point?

Do we focus too much on the paperwork, to the detriment of product and patients? Has documentation become so complex it's become a dangerous distraction and your biggest risk?

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

SETTING THE SCENE

Three years ago, I met with a site head responsible for 2,300 people manufacturing five lifesaving (critical care) medicines. The site was struggling. For every person there were five SOPs. They had more paper than people! Policies and SOPs had increased by over 1,000% in three years, but headcount had been reduced by 11%. That's right, less people – more paperwork.

SOP complexity had also increased, with SOPs averaging 34 pages. A quick assessment of readability showed 89% of SOPs were incomprehensible for the target audience. Let's pause for thought – almost nine out of ten SOPs could not be understood by the users. The site operated on shortcuts. People were forced to work around SOPs rather than follow them. They had written themselves into non-compliance. Errors and mistakes (due to procedural non-compliances) made up over 56% of deviations. Corrective actions added even more complexity to the complexity that caused the error in the first place.

When we sat down with their finance people the numbers looked bad. We calculated the cost per SOP to be approximately $12,000 and the site had to reduce costs by 32% in two years.

Don't worry, there's a happy ending! Now, three years after we worked with the client to reduce complexity, SOP numbers have reduced by 38%; deviations, errors and mistakes have fallen by 75%, and productivity is up. Cycle times have improved and they're making more product faster and rejecting far less. Right first time has improved from 67% to 98%. Staff morale has soared.

WHAT ABOUT YOU?
TAKE THE HIGHLIGHTER TEST

Documentation complexity has reached such levels it's impossible for most users to follow procedures and complete the task. They can't do both. But how do you know? Set up a **highlighter (honesty) test.**

In a room where users gather, place lots of copies of your most important SOP, plenty of highlighters and a sealed box. Leave a note asking people to highlight only what they do in practice – the instructions they actually follow – and then drop the pages into the box. Anonymity must be guaranteed.

We've done this exercise countless times to help companies simplify their SOPs. On average, 60-70% of SOP content is not followed. Just try it and see.

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DEEPER DIVE: DOCUMENTATION COMPLEXITY

For a broader perspective than the highlighter test, circulate this questionnaire to as many people as possible across your organization, particularly document users.

		YES	NO
1	Are your policy documents kept simple (no more than 3-4 pages) and issued only after consultation/input and adjustment from users?		
2	When new regulations arrive, do you consult with users before updating your policy guidance?		
3	Are users allowed to interpret policy (standards) locally to meet local/regional needs?		
4	Have you calculated cost per SOP and the total investment put into your documentation system?		
5	Are all SOPs written by the users for the users (not the regulator)?		
6	Do you routinely use the Gunning Fog or Flesch-Kincaid indexes to assess readability for users?		
7	Do your SOPs have more pictures/schematics than words?		
8	Do you test usability of SOPs in the workplace before implementation?		
9	Do you actively prevent CAPAs adding detail to SOPs following a mistake or error?		
10	Do you routinely conduct the highlighter test?		
11	When auditors/consultants/regulators/customers insist on more detail, do you challenge or push back?		
12	Do you make it difficult for people to write new SOPs or amend old ones?		
13	Do you focus on educating your people, rather than training them, by explaining the 'why' more than the 'how to do'?		
14	Have you banned the 'read and understand' approach to training?		
15	Are you investing in video/YouTube technology to replace words/paper?		
16	Is simplification your company's top priority and do leaders walk the talk?		
17	Do you use intelligent risk assessment to decide what goes into/stays out of documents rather than putting everything in 'just in case'?		
18	Do you routinely run simplification FedEx days? (If you've never heard of this, answer no and give us a call for more information). These are vital if you're committed to simplification.		

So, has your documentation become more important than your patient? If you answered yes to most questions, you're in good shape. Lots of no's? You could be in trouble.

WHAT YOU CAN DO: YOUR SIMPLIFICATION ROAD MAP

The site we mentioned was able to turn it around and stay in business because they followed these four *very hard* steps – our simplification road map. Adding complexity is easy and requires very little thinking. That's why we add complexity in the first place. Simplification is the opposite, it takes brains, blood sweat and tears.

Step One:
CREATE THE INTRINSIC MOTIVATION

Everyone, from the senior leadership team to the shop floor, must be totally committed. Simplification is not a project, but a way of life. Without a 'what's in it for me' people will just give up. We spent three to four days getting the entire site to understand that simplification = survival.

Step Two:
EATING THE ELEPHANT ONE BITE AT A TIME

With thousands of SOPs, where do you start? By using Pareto's principle (or the 80/20 rule), which states that 80% of your risk is due to 20% of your SOPs, or there about. By talking to users and looking at quality metrics, we identified just over 800 high-risk SOPs. Over many months we then boiled this down to 202 using the highlighter test.

Step Three:
LET THE USERS LOSE – FEDEX DAYS

FedEx guarantees delivery in one day. We assigned each SOP to a smart, dedicated group of four to five users and asked them to deliver a drastically simpler version – by the end of the day. To prepare them, we trained each group in many of the tools and techniques in our simplification toolkit (below).

Step Four:
STOP COMPLEXITY AT THE SOURCE

Preventing complexity is a lot easier than removing it. We focused on:

> Ensuring the change control system filtered out change requests that added complexity

> Redesigning the deviation and CAPA system so it focused on prevention, not correction

> Training people on how to conduct simplification audits

> Redesigning the SOP system to prevent complexity being added by co-authors and agreeing to KISS (keep it simple, stupid!) rules for SOP design, creation and content

Tip: You could also consider creating SOPs as videos. What do you do if you need to look up how to do something around the house? You go to YouTube. Other industries use video, so why don't we?

Your Simplification Toolkit all resources are available in our online resource library – **www.nsf.org/info/pblibrary**:

White Paper:	Are You Facing a Complexity Crisis	White Paper:	Changing Your Quality Culture and Improving GMP Behaviors: What Works and What Doesn't
Webinar:	The Art and Science of Simplification – How to Win Your War on Complexity	White Paper:	How to Use B = M.A.t.H
		Video:	How to Jumpstart Your Pharma Business by Simplifying Processes

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Your Call to Action:

> Start now!

> Do the highlighter test

> Circulate the questionnaire – are you at risk?

> Follow our simplification road map and start using our simplification toolkits

> Get in touch with us at **pharmamail@nsf.org** with questions

Live System Assessments
Why Do Them?

by Rachel Carmichael, Executive Director, Pharmaceutical Services, NSF International

> I have a vivid memory of a certain "pre-exam stress" period as my old production site prepared for my first regulatory inspection in the early 1990s. The theory, even then, was that we would be *continuously inspection ready* but that didn't stop us from wanting to ensure that we presented our best face to the inspectors.

We would pre-run the obvious tasks, including ensuring that we could create a summary report of the last two years' worth of deviations encompassing all departments and all the stages of the events. This is dynamic data in an ever-changing database. Depending on how you requested the search, certain events could be included or excluded. Our endeavor was to make sure that all events were there.

After nearly 10 years in a production environment I became an Inspector for the MHRA and spent nearly 11 years seeing how other companies handled their inspections. The vast majority had done some preparation. Normally the first part of the inspection will include a review of the deviation system. The companies where the staff knew what they were doing would prepare a summary report of the last two years' worth of deviations and we would select a small number of reports to review in detail. Not long after I'd started, I had cause to become rather suspicious of the prepared reports and so I became rather more interested in the search criteria that had been put into the databases to define this so-called 'comprehensive report'. I started to ask for the reports to be rerun on that day, not necessarily to be reprinted, but certainly to look at any differences. On more than one occasion I found that certain departments had been omitted. Was that intentional? Only the hosts can ever say.

Regulatory Background

The idea that a company can "manage" an inspection or an inspector is either overly optimistic or at the very least naive. In Europe, where the production and storage sites are licensed, the refusal of an inspection, or failing to respond to inspectors' requests, can result in the license being taken away surprisingly quickly. I found that it was a very rare event for me to have to take out my warrant card and remind people of their legal obligations to comply with the inspection process. That said, I never had to do it twice.

Since 2012 the U.S. has had stronger legal grounds to deal with people that *"delay, deny, limit or refuse an inspection"* through the Food and Drug Administration Safety and Innovation Act (FDASIA). In the guidance that was issued in October 2014 to accompany that Act, companies should not limit access to company records from the FDA: Section V, sub part C, Limiting Access to or Copying of Records.

If found to be in contravention of these requirements a company may have their product considered adulterated. For U.S.-based companies this may take some time to play out in the courts but for overseas companies an import alert can be placed very quickly. The FDA procedures governing the review of electronic records are published in chapter 5 of the FDA Investigations Operations Manual (IOM) available on the FDA website.

Particularly of interest is section **5.3.8.3.2 – ELECTRONIC DATABASES AND QUERIES** which highlights the concern around the accuracy of such transient queries in dynamic data from an ever-changing database, and instructs inspectors:

> *"You must assume the query logic is not validated and take appropriate action to ensure the data is accurate and no data has been accidentally omitted due to a programming logic error."*

Clearly, relying on printouts from such databases is an inherently weak approach and inspecting directly in such systems is far more efficient. This same section clarifies that "Reviewing data contained in electronic

databases is generally most effectively accomplished with the use of a computer" and gives the following guidance when it is necessary to access a firm's data during an inspection:

> Oversee the firm's personnel accessing their system and have them answer your questions

> Request the firm run queries specific to the information of interest

> Request the firm provide the parameters used to generate the data

> Request the firm to copy the data to electronic storage media

As more and more companies and organizations moved to comprehensive electronic quality management systems (eQMS) (such as QPulse which is extensively used within the UK NHS), the need to inspect directly in the electronic systems increased. These systems hold all the procedures, all the training relating to those procedures and all the elements of the pharmaceutical quality system that you would expect to see; deviations, change control, risk management, audit program.

Qualification Requirements

Clearly the systems should be qualified. Many organizations contract out this activity but the responsibility for its suitability for use within our type of environment stays with the user. While there may be an installation and operational qualification from the provider, the performance qualification should be done by the organization. It should ensure that your system works as intended within your network and environment, and meets compliance requirements including those for data integrity. During the operational qualification the procedures for use should have been developed and these should be used during the performance qualification. Many companies develop good procedures for how to use the system but are tempted to take a more flexible approach with regard to the administration of the system and make statements like "refer to the administration team" without actually being clear as to what they are meant to do and how.

Potential Outcomes

Sensible companies will also have specific information regarding reporting. A number of systems have predefined reports and also allow the company to run ad hoc reports. The failure to control this was evident at one of my inspections where the organization had not realized that the predefined reports were present in their comprehensive eQMS. When we ran the reports, live, during the inspection, we produced metrics significantly different from the official metrics for the site. The live reports identified that very few staff had conducted the required confirmation for training in the procedures. Furthermore, the reports identified that large numbers of documents were considerably past due for review and that deviations were being re-scheduled constantly with, effectively, no oversight. In less than five minutes we had established the lack of control of their operation and that management review was fundamentally flawed, being based on incorrect (sanitized) data.

Preparation – Your Essential Tips

For companies with such systems, recognize that one day your inspector will want to audit live in the system. It is common practice now. To prepare for such live system assessments, your own self-inspection program should adopt the same approach.

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In preparation, consider the following:

> Know which of your systems are likely to be inspected in this way – eQMS; any of the individual quality systems such as your deviation system, change control, complaints and training; and shop floor electronic systems and laboratory systems

> Make sure you've identified staff who are capable of hosting such an exercise. You need the super users to be able to demonstrate the system and the reports. You do not want people hosting that are unfamiliar with the capabilities of the system.

> • *Remember that, even for custom systems, you have no idea what your inspector knows.*

> Conduct internal audits live in the systems. Make sure your routine challenges and checks challenge the way in which the systems could be looked at. It is possible that the system administrators have not had to face inspectors, so these practice events are key.

> Ensure that you understand the automatic reporting built into the systems. Be prepared to explain any potential differences that the live system reports may generate compared to your official metrics.

If you're not used to going directly into electronic systems remember that your inspectors can be very familiar with large numbers of different systems, have no fear about looking at another electronic system and adopt approaches that are very open and so cannot be "managed".

Watch Out!

Make sure that your IT department understands it may have to support the site during inspections and that this is a company priority. I once had a surreal experience where the IT department (in a very large organization) declared that they were a corporate group and were not required to assist a site and the person that could have helped went home!

Useful Resources

A site that has good control of its data integrity will be in a stronger position to withstand this type of inspection and your starting point should be the *PIC/s guidance (currently Draft v3), Good Practices for Data Management and Integrity In Regulated GMP/GDP Environments.*

Looking more holistically, in 2016 the *ISO 9001 Auditing Practices Group issued Guidance on Electronic Documented Information Systems.* This document gives "general guidelines for the conduct of audits of management systems that are either fully electronic-based or have a high degree of documented information in electronic media". Although it is intended for people who have wide-ranging experience of these types of audits, it was written to be accessible to those who do not and should be suitable for internal audits. The document takes you through planning for your audit, review of documented information, on-site operation activities and auditing the control of electronic documented information. In addition, it touches on resources, electronic communications, multisite management systems and auditor competence.

Conclusion

It's important to recognize that a live system assessment inspection is going to happen. Preparation is key. Understand your systems and reporting capabilities, your key staff and their likely capability when under the full focus of inspectors, and above all practice and challenge your systems – do not have blind faith! We are here to help if you would like an external challenge of your systems. Contact us at **pharmamail@nsf.org**.

Further useful resources are available in our resource library – **ww.nsf.org/info/pblibrary**:

> Webinar: How to Install a Data Governance Process from Ground Zero

> White Paper: Data Integrity – A Closer Look

> Webinar: Regulatory Perspectives on Data Integrity

> Case Study: How to Correct an Unexpectedly Difficult GMP Inspection and Prevent a Relapse

Words of Wisdom From Anders Vinther

Industry Talk Time With Martin Lush

In this new feature, Martin Lush talks with a veteran pharma professional to get their point of view on the industry and beyond.

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

Anders' Words of Wisdom

> Work hard to understand the business, not just your job.

> If you're not operating outside your comfort zone 30% of your time, change jobs. When your day becomes routine, it's time to change.

> NEVER forget you are in the public health business. If you do, you become part of a very big problem.

> In every decision focus on doing what's right for the patient.

> If you have a problem, consult Google/ Amazon. Most of the problems we face are not new. Make reading a habit and part of your job.

Anders' Bio

> Current Site Head and VP Quality at Intarcia: Work includes preparing the company for its first NDA and launch of a new technology.

> Chief Quality Officer at Sanofi Pasteur: Work included culture change across multiple sites in multiple countries.

> VP Quality at Genentech and Roche: Work included developing one quality system across all manufacturing sites worldwide and integration of Roche and Genentech.

> Cofounder and Chief Quality Officer at CMC Biologics: Work included building and growing a company from scratch including construction, qualification and approval of green field facility. The company was successfully sold a few years back.

> VP Quality at Novo Nordisk.

> Very active at PDA including past Chairman of the Board of Directors.

ML: **Anders, after 30 years in pharma, if you had your time again, would you do anything differently?**

AV: I don't think so because I've been fortunate to experience so much, from leading culture change in a multinational company, to integrating two large businesses, to building a business from scratch.

ML: **You make it sound like this was all down to being in the right place at the right time. Did you have a career plan?**

AV: To be clear, none of this was down to luck! Although I didn't plan my career, I've always pushed myself outside my comfort zone. One piece of advice I would give is learn as much as you can about the business as soon as possible. Organizations tend to put people into silos and keep them there. If you start in R&D, you stay there. The same for QA, manufacturing, technical support... the lot, in fact. It's important to understand the world of finance, purchasing, logistics, sales and marketing, not

just your job. Become obsessed about learning what others do and build strong networks. As your career progresses, you will need both.

> *"Lots of problems I have seen in my career have been due to lack of organizational intelligence where decisions are made without thinking about the impact on others. So, get out of your silo and talk to others to better understand the business and their world."*

This is important for QA professionals who have, in my opinion, become conditioned to be reactive, rather than proactive. When you understand how the business works, you can figure out how you can add value. To do this you need to talk the language of business, not compliance. QA should be focusing on error prevention, simplification, process design and other value-adding activities, not just the reactive stuff.

ML: Any other career advice?

AV: Yes, three things. Firstly: Don't change jobs too soon and don't stay too long! It takes at least two years to understand your job before you can make a real contribution. First you learn and then you give back. If you move too soon, you have not contributed to the business; if you move too late, you are taking up somebody else's job opportunity.

My second piece of advice: If you're not being challenged, if you're not learning something new every day, if you're not operating outside your comfort zone at least 30% of the time, change roles.

My last piece of advice is the most important:

NEVER forget you are in the public health business. If you do, you become part of a very big problem. Remember, every decision you make potentially impacts a patient.

ML: What have been some of your greatest challenges and what did you learn from them?

AV: There's one in particular. During my Genentech days we observed Leptospira as a contamination during fermentation, a difficult-to-see, slow-growing spirochaete capable of squeezing through a 0.2-micron filter. The experience was memorable because it forced us to think outside the box and challenge conventional thinking. At the time everyone thought a 0.2-micron filter would stop everything. We decided to share it with the world because it is related to patient safety and no other company knew about this potential issue. From a patient's perspective, it's a shame companies don't share their problems more openly so we can all learn rather than repeat the same problems.

ML: You've faced a lot of high-pressure situations in your career. How did you cope? Any recommendations?

AV: Yes, just keep the patient foremost in your mind and focus on doing the right thing for them. I found this gave me great clarity. My career in pharma has been dominated by grey area decisions where you simply don't have all the facts. Remember, rejecting a batch because you're not quite sure can also have severe consequences – the patient is not getting their medicine.

> *"I always imagined justifying my decision to a patient sat opposite me or my products being taken by family members. I have also believed in total transparency with regulators when making the tough decisions. This transparency leads to trust. Being secretive leads to the opposite."*

Words of Wisdom

ML: **What do you think the industry will look like in 2030 and how should companies prepare?**

AV: Martin, I have heard you describe the pharma industry as one driven by 21st century science, managed by 20th century minds and regulated by 19th century laws and regulations. I totally agree! It will continue to be difficult to implement new technologies because of the global regulatory complexity. Regulatory agencies must understand they are, collectively, slowing down innovation and indirectly causing drug shortages because of this complexity.

However, one of the most progressive people I've ever met is FDA's Janet Woodcock, so who knows. I am also member of a group of QA senior leaders from the top 25 pharma companies working collectively to share problems and generate solutions. We need more collaboration of this type if we're to meet future health care needs.

ML: **Anders, I know you read a lot. What would your top five recommendations be?**

AV: I was struggling to get it down to five, but here they are:

> *The New Economics* by Edward Deming. Although a renowned statistician, all his books focus on the importance of people, not numbers.

> *Accelerate* by John Kotter. If you want to change culture, this is a must read.

> *Influencer* by Patterson and others. If you want to influence without authority, this is the book for you.

> *Switch* by Chip and Dan Heath. A great read if you want to change behaviors and culture.

> *The 7 Habits of Highly Effective People* by Stephen Covey. No reading list would be complete without it. You can read this classic again and again and still find something new.

"So many of the challenges facing our industry are not new. The solutions have already been figured out. Just ask Amazon."

ML: **If you were cast away on a desert island, what piece of music would you take with you and why?**

AV: If you let me take an album it would have to be Queen's Greatest Hits. Why? Because I would never tire of listening to it!

AV: **OK, my turn, what would you take?**

ML: I would take Vaughan Williams' Lark Ascending. Why? It instantly takes me back to the North York Moors. I can be in a taxi in New York or in a hotel in Shanghai but after the first few chords, I'm instantly transported back home without getting on an aeroplane.

ML: **Anders, in terms of your hobbies and interests, what do you do and why are you passionate about them?**

AV: My number one hobby (which is also a business) is wine making. I am a wine maker, and my wife and I have a winery – Flying Suitcase Wines. I love the process from harvesting the grapes at the crack of dawn to running tasting sessions for my customers. Living in California helps!

Words of Wisdom

Drug-Device Combination Products

The EU Medical Devices Regulation (MDR) 2017/745, which replaces the existing medical devices Directives 93/42/EEC and 90/385/EEC and amends the medicinal products Directive 2001/83/EEC, will apply from 26 May 2020.

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

& Laurence Matheron

The MDR, amending Directive 2001/83/EEC, clarifies the definitions of products with a medical purpose to determine whether the products are regulated as medicinal products or medical devices depending on their principal intended mode of action. The mode of action for medicinal products is primarily pharmacological, immunological or metabolic, while the mode of action for medical devices is primarily physical or mechanical.

If the principal intended action of the drug-device combination products is achieved by the medicine, the entire product is regulated as a medicinal product under Directive 2001/83/EC and Regulation (EC) No 726/2004 (for centrally authorized products).

Since the beginning of 2019, the EMA has published two documents in relation to this new regulation and the expectations for manufacturers of drug-device combination products:

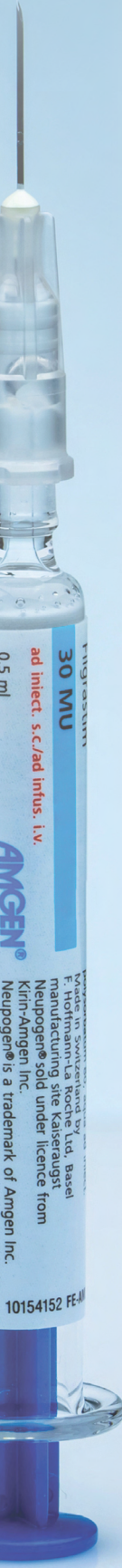> A Q&A guide on implementing the MDR published in February 2019

> A guideline for public consultation on the quality requirements for drug-device combinations published in June 2019

Two types of drug-device combination products are defined in the MDR:

> Integral drug-device combinations: The medicinal product and the medical device form a single integrated product. Two types of integral drug-device combination products are defined:

• Any device that incorporates, as an integral part, a medicinal product where the action of that substance is principal and not ancillary; e.g. a drug eluting intra-uterine device

• Any device that is intended to administer a medicinal product, in such a way they form a single integral product intended exclusively for use in the given combination and which is not reusable; e.g. a pre-filled syringe

> Non-integral drug-device combinations: The medicinal product and the medical device are separate items, but they are combined for administration of the medicine. They can be co-packaged or obtained separately. These devices should be CE marked.
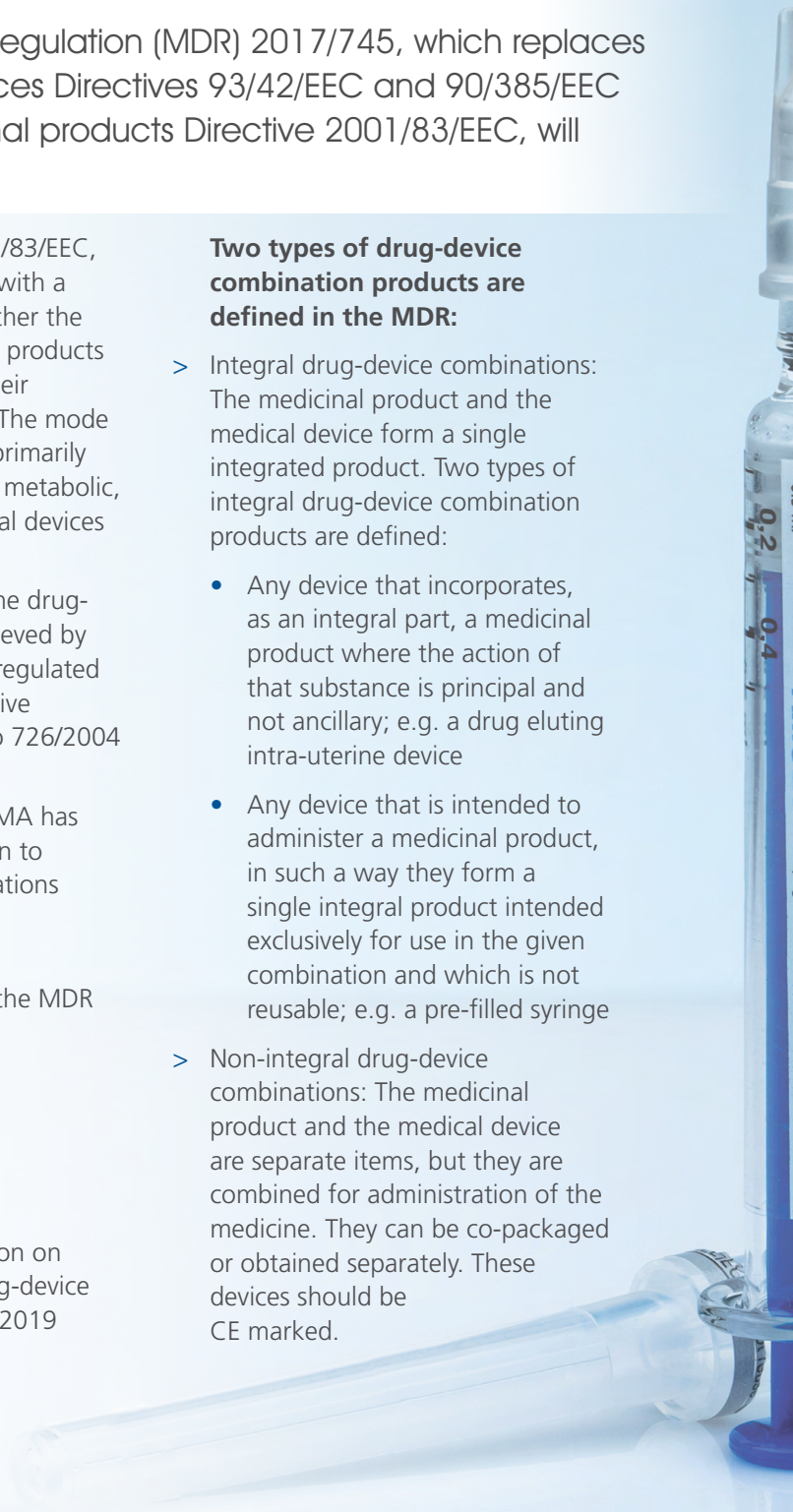
In case of integral drug-device combinations, there is a new requirement described in article 117 of the MDR that amends Annex 1 of the medicinal products Directive 2001/83/EEC. The marketing authorisation application for medicinal products that incorporate a device component as a single integral final product will need to:

> Include, where available, the **results of the assessment of the conformity of the device part** with the relevant general safety and performance requirements […] contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body

> **If the application dossier does not include the results of the conformity assessment** […] and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required […], **the authority shall require the applicant to provide an opinion on the conformity of the device part** […] issued by a notified body […]

For integral drug-device combinations already authorized or those submitted before the date of application of the MDR (26 May 2020), the requirement of article 117 is not applicable, except if manufacturers make substantial changes to the design or intended purpose of the device component or introduce a new device.

EMA published on June 3, 2019, a draft guideline on the quality requirements for drug-device combinations including the manufacturing and control methods. This draft guideline:

> Covers integral drug-device combinations and non-integral drug-device combinations

> Applies to drug-device combinations where the medicinal product constituent is a chemical, biological or radiopharmaceutical

> Clarifies what is expected in the quality part of the dossier for a marketing authorisation application or a variation application

> Contains a template for the notified body opinion on the conformity of the device to the relevant general safety and performance requirements described in Annex I of the EU medical device regulation

A marketing authorisation application for a drug-device combination should include:

> A demonstration of compliance with any relevant European Pharmacopeia chapters or monographs

> Structured information on the device:
  • Relevant to the quality, safety and efficacy on the medicinal product
  • Demonstrating compliance of the device with MDR Annex I
  • Related to manufacture, control and usability of the device drug combination as defined for the intended patient population

> A discussion and justification for the use of platform technology/technologies

The specific requirements for what should be included in marketing authorisation applications (with reference to the modules of the eCTD) for integral drug-device combinations and non-integral drug-device combinations are provided in chapters 5 and 6 of the draft guidance. Chapter 6 differentiates a non-integral drug-device combination with co-packed medical devices and a non-integral drug-device combination with separately obtained devices.

EMA specifies that this guideline will increase transparency and consistency of information in regulatory submissions, reducing work for all stakeholders and ultimately improving patient safety.

Contact us at **healthsciences@nsf.org** if you have any questions on the article.

U.S. FDA/EMA REGULATORY INSPECTION AND ENFORCEMENT TRENDS

by Lynne Byers,
Executive Director,
Pharmaceutical
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International

NSF provides expert GMP advice, on demand, to insurance company Munich Re (www.munichre.com/landingpages/corporate/en/equip.html) when it is assessing the risk of insuring a client. Like the pharmaceutical industry, the insurance industry must review regulatory trends in order to understand them. The FDA Shutdown and Import Bans graph (*Figure 1*) is based on 10 years of publicly declared enforced and voluntary facility shutdowns. Munich Re performed an in-depth review of U.S. FDA 483s issued to drug manufacturers between 2009 and 2017. To complement this work and to compare it with the EMA's findings, an assessment was also made of the publicly available data from EMA regulatory authorities using the EudraGMDP database of non-conformance reports. As the information provided in EudraGMDP is a summary of findings, it is not possible to perform the assessment in the same way as the U.S. FDA data. However, both sets of data provide a good insight into the findings from these agencies.

The data provide the following insights:

> Both the FDA and EMA have the highest number of import bans/non-conformance reports from sites in China and India (*Figures 1 and 2*).

> Emerging trends from FDA drug inspections (*Figure 3*) affect:

  • Procedures, both availability and use in QC, production, cleaning, maintenance and process controls (essentially the lack of a Pharmaceutical Quality System)

  • Lack of scientifically sound test methods

  • Inadequate investigations

  • Cleaning and sanitation

  • Training

> Emerging trends from EMA inspections (*Figure 4*) affect:

  • Pharmaceutical Quality System

  • Production

  • Documentation

  • QC

  • Premises and equipment

The findings from both regulators are unexpectedly very similar.

FDA Shutdowns + Import Bans (2009-2017)

U.S. 48, India 48, China 43, Europe 25, Canada 13, Mexico 7, Australia 3, Brazil 3, Tunisia 2, South Korea 2, U.A.E 2, Turkey 1, Thailand 1, Hong Kong 1, New Zealand 1, Jamaica 1
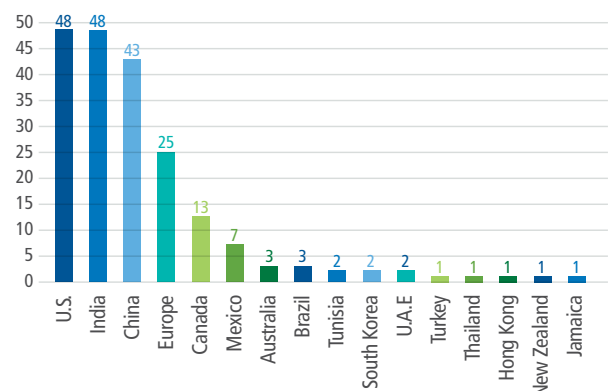
Figure 1

EMA Non-compliance Reports by Country (2010-2017)

India 48, China 38, UK 10, U.S. 4, France 3, Spain 3, Italy 2, South Korea 2, Syria 2, Bangladesh 1, Bulgaria 1, Jordan 1, Romania 1, Saudi Arabia 1, Taiwan 1, Thailand 1

Figure 2

Questions managers need to ask themselves:

> Do we have clear procedures for all necessary activities, which are easily understandable and followed by all staff?

> Do we have sufficient numbers of staff to perform activities and operate under control?

> What evidence do I have to support my assessment that my site is under control?

> Are staff sufficiently trained and educated in the activities they perform?

> Do we understand what is required to operate in compliance with data integrity requirements?

> Is my environmental monitoring program linked to my contamination control strategy?

> Do we have plans in place to meet the proposed Annex 1 of EudraLex Volume 4?

> Are the cleaning methods used still appropriate?

> After reading this article and reviewing the data, WHAT ACTION DO I NEED TO TAKE?

Top 15 Deviations cited on FDA 483s (2006-2017)

Deviation	Number of observations
Equipment design, size and location	573
Procedures for sterile drug products	575
Lack of written stability program	601
Prepared for each batch, include complete information	630
Calibration/inspection/checking not done	683
Training operations, GMPs, written procedures	689
Cleaning/sanitization/maintenance	764
Testing and release for distribution	773
SOPs not followed/documented, cleaning and maintenance (21 CFR 211.67(b))	788
SOPs not followed/documented, production and process control (21 CFR 211.100(b))	808
Control procedures to monitor and validate performance	895
Absence of written procedures, production and process control (21 CFR 211.100(a))	1069
Investigation of discrepancies, failures	1252
Scientifically sound laboratory controls	1265
Procedures not in writing, fully followed, QC (21 CFR 211.67(b))	1873

Figure 3

EMA Findings by Eudralex Volume 4 Part 1 | Chapters and Annexes

Chapter/Annex	Number
Biologicals (Annex 2)	
Retention samples (Annex 19)	
QP certification (Annex 16)	
Outsourced activities (Ch 5)	
CSV (Annex 11)	
Sterility (Annex 1)	
Personnel (Ch 2)	
Qualification and validation (Annex 15)	
Premises and equipment (Ch 3)	
QC (Ch 6)	
Documentation (Ch 4)	
Production (Ch 5)	
PQS (Ch 1)	

Figure 4

View our related learning resources – **www.nsf.org/info/pblibrary**:

> Video: Introduction to Pharma Data Integrity eLearning

> Webinar: How to Write a Contamination Control Strategy for Your Facility

WHAT NOT TO SAY DURING AN INSPECTION
– In Five Easy Parts

We understand nerves run high during an inspection but do yourself a favor and avoid some things commonly said to inspectors. This round-up includes comments our experts have seen or heard during their years of experience working in the pharma industry.

WHAT NOT TO SAY TO AN INSPECTOR

"How are things at the FDA nowadays?"

"How long have you been working as an inspector?"

"Maybe it is a mistake…"

"I disagree."

"What's your opinion?"

"You should have seen it before the improvements!"

"It depends."

"Our previous inspector told us to do it."

WHAT NOT TO SAY ABOUT YOUR PROCESSES

"Our company policy does not allow inspectors to see our supplier audit reports."

"We usually do it that way."

"We don't normally operate like this."

"We have a workaround because it doesn't work as written."

"But we've always done it that way."

WHAT NOT TO SAY ABOUT YOUR MANAGEMENT

"We disciplined the employee who committed this mistake and next time he'll be fired."

"Corporate is responsible for that."

"We don't have the key for that."

"You're not allowed to see that – we can't let you in there."

WHAT NOT TO SAY ABOUT YOUR PEOPLE

"We have had a lot of turnover lately."

"We just started a second shift and I don't think they are well trained yet."

"Our training system needs an overhaul."

WHAT NOT TO SAY ABOUT YOUR FACILITIES

"The cases of wine belong to the managing director."

"The lunch boxes and ice creams in the pharmaceutical fridges belong to staff."

"We don't really know who has the keys to our buildings."

Have your own inspector stories to share? Send them to **healthsciences@nsf.org** and we'll include them in the next Journal.

Regulatory
Update

Pharma EU News

EU-USA Mutual Recognition Agreement

The schedule for implementing the EU-USA mutual recognition of inspection agreement (MRA) was met with the final EU Member State, Slovakia, being approved by the FDA on July 11, 2019, four days before the July 15 deadline.

Therefore, the MRA is now fully operational, which means that product imported from the USA is no longer required to be re-tested on importation into the EU. Discussions are still ongoing as to the applicability of the MRA to pre-approval inspections (PAIs) and to veterinary products even though these should have been determined by the July 15 deadline. The applicability to blood products and vaccines is not due to be resolved until July 2022.

Aide-Memoire on Compliance with FMD Safety Features Requirements

The European Commission has published an aide-memoire on compliance with the safety features provision of the Falsified Medicines Directive and the associated Delegated Regulation 2016/161. This guide provides information for manufacturers and assists inspectors when conducting audits.

The nine-page guide consists of a series of operational areas or items, each with a series of questions to ask or things to see and, where applicable, the appropriate references in Regulation 2016/161 or the GMP guidance.

Medicine Shortages

In July 2019 the European Union task force, set up to address problems with medicines' supply, published two documents:

> Guidance for marketing authorisation holders on reporting of shortages in the EU

> Good practice guidance for communication to the public on medicines' availability issues

The task force was established by EU regulators to better address potential problems with medicines' supply and to develop and coordinate actions to facilitate the prevention, identification, management of and communication about shortages.

Both documents lay the foundations for an improved and harmonized EU approach in reporting of and communication on medicines' shortages and availability issues, a key public health priority for the EU network.

BP and USP MoU enter a formal partnership

The British Pharmacopoeia (BP) and United States Pharmacopeia (USP) signed a Memorandum of Understanding (MoU) in Washington D.C. on July 26 2019. The agreement will enable improved collaboration and knowledge sharing between the BP and the USP in a wide area of standards setting for medicines. One of the features of this agreement is the commitment from both organizations to provide opportunities for exchange of staff and participation in events and joint working relationships.

Pharma EU & ICH Updates

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

Regulatory
Update

Pharma US Updates

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

Brexit – Medicines

The uncertainty as when, or even if, the UK will leave the EU continues. At the time of writing the new deadline is October 31, 2019. In the meantime, the positions regarding medicines remains unchanged from the pronouncements made by both the EU and the UK prior to the previous deadline of March 29, 2019.

ICH News

The ICH continues to expand; as of June 2019, there are 16 members and 32 observers, with Argentina (ANMAT), Israel (CPED), Jordan (JFDA) and Saudi Arabia (SFDA) having been added as observers.

At the June 2019 meeting in Amsterdam, the drafts E8 (R1) General Considerations for Clinical Trials and ICH M10 Bioanalytical Method Validation received step 2b approvals and are now receiving their public reviews (step 3).

It was reported that Q12 has made good progress. The latest working draft has modified some of the contentious elements of the Established Conditions section by removing the distinction between intrinsic and extrinsic established conditions and all reference to key process parameters (KPPs). The expert working group say they hope Q12 will reach step 4 approval at the next ICH meeting in Singapore in November 2019, but this does require the European Commission to have resolved its issues with the compatibility of some sections with EU law by then.

Also, at the ICH meeting in June 2019 it was agreed to begin working on the following topics:

> A revision of ICH Q5A, Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

> A new guideline, Q3E, on Impurity, Assessment and Control of Extractables and Leachables

Pharma US News

Voluntary Recalls – FDA Guidance on Process and Procedures

In April, FDA issued a new guidance, Initiation of Voluntary Recalls Under 21 CFR Part 7, Subpart C, aimed at strengthening the voluntary recall process used to remove defective or potentially harmful products from the market. The new guidance focuses on three areas: **training** to staff and an emphasis on having an effective recall communication plan, **record keeping** with focus on improving traceability and promoting use of modern approaches such as blockchain technology, and **procedures** to minimize delays once a decision for recall has been made.

Biosimilar Development – Final Guidance on Demonstrating Interchangeability

In a continued effort to promote competition in the biologics market to lower costs, with 19 biosimilars licensed as of May 2019, FDA issued a final guidance on demonstrating interchangeability with a reference product. It includes detail on how to address the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product, to meet the BPCI Act requirement for interchangeability of biologics that are administered more than once. It is hoped that the issue of this guidance together with reclassification to biologics under the BPCI Act of certain products, such as insulin, that will take effect March 2020, will lead to increased competition and lower cost for patients.

Project Facilitate – Expanding Access to Investigational Therapeutics for Cancer Patients

In June, the FDA's Oncology Center of Excellence announced a new pilot program, Project Facilitate, to assist oncology health care professionals in requesting access to unapproved therapies for patients with cancer.

Project Facilitate will be a single point of contact where FDA will help physicians through the process to submit an expanded access request for an individual patient. This initiative, together with recently issued FDA guidances encouraging companies to broaden their eligibility criteria to allow more patients with cancer to participate in clinical trials, should promote access of investigational therapies to patients with cancer.

Labeling – Draft Guidance on Drug Abuse and Dependence Section

FDA announced a new draft guidance in July, Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products – Content and Format. The objective of this guidance is to ensure that information in product labeling on abuse, misuse, addiction, physical dependence and tolerance is clear, concise, useful and informative. The guidance includes detail on presentation of abuse-deterrent properties, if applicable, and how to present information where possible within, and across, drug and therapeutic classes.

EU MDR and IVDR News

Since June 2019, the EC has published an FAQ on the Unique Device Identification (UDI) system. There was a call for observers to sit on the Medical Device Coordination Group (MDCG) nomenclature subgroup, which is now closed. In addition, the Commission announced that there will be a call for experts to sit on panels to support the assessment

of specific high-risk devices and to contribute to the prospective improvement of the overall regulatory framework.

The following guidance documents were released by the MDCG and are available on the European Commission website:

> MDCG 2019-6 Q+A: Requirements relating to notified bodies

> MDCG 2019-7 Guidance on Article 15 of the Medical Device Regulation (MDR) and in vitro Diagnostic Device Regulation (IVDR) regarding a 'person responsible for regulatory compliance' (PRRC)

> MDCG 2019-8 Medical Devices: Guidance document Implant Card relating to the application of Article 18 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices

Four Notified Bodies are now designated for the MDR. The list can be found on the European Commission website.

Brexit – Medical Devices

In June 2019 the European Medicines Agency (EMA) released for public consultation a guideline on quality requirements for regulatory submissions for medicines that include a medical device (drug-device combinations).

In readiness for a no-deal Brexit, the MHRA published an amended regulation: The Human Medicines (Amendment etc.) (EU Exit) (No. 2) and the Medical Devices (Amendment etc.) (EU Exit) (No. 2) Regulations 2019. These regulations come into force immediately before exit day.

EU MDR and IVDR Updates

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

Regulatory Update

NSF News…

NSF Participated in Artificial Intelligence Workshop at the Enquete-Commission in Berlin

NSF International took part in an artificial intelligence workshop at the Enquete-Commission on May 13 in Berlin, Germany. The commission was set up by the German Bundestag to address growth, prosperity and quality of life. Oliver P. Christ reported to the AI Committee as an expert on the future regulatory requirements for AI in medical devices and health care. NSF is working on AI as the dominating topic for the future.

NSF MILESTONE 300TH QUALIFIED PERSON

"One of my absolute pleasures is to observe the trainee QPs on their individual journeys from enquiry to viva prep sessions to eventually hearing about their success at viva assessment.

Everyone has their own journey, and their own challenges. It is one of the best aspects of job satisfaction for me to see those journeys unfold and watch the individuals develop and reach their potential. The final element is to see them come to the QP alumni meetings, sharing stories and experiences, or even becoming sponsors, assessors or inspectors in the future.

We are here to guide on those journeys, and it was a privilege to be part of Dan's journey, so congratulations to Dan and to those who came before and to those who will come after."

Mike Halliday, Executive Vice President, Pharmaceutical Services, NSF International.

"My QP journey started in early 2015 with Mike Halliday inducting me and a handful of other new starters into the NSF family with a cautionary presentation on what to expect en route to the QP viva. It wasn't supposed to be dissuasive, but rather a reality check on the work-life balance sacrifices that would be needed, and a head's up on the emotional ups and downs that lay ahead. My journey, it turned out, would not be particularly unique.

Along the way, I learned the ways of the parrot, with recurring phrases like "it depends" and "risk assessment" now firmly in my arsenal. I became a master of the flip-chart and a marker-pen maestro. And, I learned how to adeptly navigate the grey zones of GMP conundrums. But, perhaps most importantly, I made new friends, drinking buddies and a network of QPs to tap into for advice (or jobs) whenever the need might arise: a truly valuable asset.

It was challenging, fun, rewarding, sometimes stressful, but ultimately successful: on 17 April 2018, I entered the arena at Burlington House, London (the home of the Royal Society of Chemistry), battled the QP viva panel and emerged victorious, a Qualified Person. Little did I know at the time, but this wasn't only a personal landmark, but a landmark for NSF too – lucky #300, I suppose!"

Daniel Powell.

Health Sciences Podcasts Live on Spotify and the App Store

Going for a run? Walking the dog? Why not learn along the way! We are excited to announce that our series of medical device and pharma podcasts are now live on the Apple App Store and Spotify (available on iPhone and Android). Search "NSF Health Sciences" today. You will find podcasts on some of our latest pharma white papers and webinar recordings, and we are looking to develop our podcasts even further.

Robert Smith Awarded Fellowship by the Royal Pharmaceutical Society

NSF associate Robert Smith has been awarded a fellowship by the Royal Pharmaceutical Society for his services to the Society as a QP assessor, for being Vice Chair of the Society Panel of the Assessors and for work as a QP to find solutions when releasing ATMPs.

NSF's Robyn Meurant Participated in a Panel Session on Notified Bodies at the MedTech Forum

Robyn Meurant, Executive Director, Regulatory Services, IVDs and Medical Devices at NSF International, joined a MedTech panel on May 15 in Paris to discuss the readiness of notified bodies in time for the May 2020/2022 deadlines.

The session, Notified Bodies: A Key Pillar of the New EU Regulatory System, provided insight into the key challenges notified bodies and the industry are experiencing as the deadlines of the new regulations approach. The multi-stakeholder panel explored solutions that might be put in place to address these challenges. You can view the full news item on **www.nsfmedicaldevices.org**.

Relocation of NSF International's Expanded Shanghai Laboratory

NSF's testing laboratory in China moved location earlier this year, with a relocation ceremony taking place on June 14 in Shanghai. The new laboratory, with expanded space and equipment, will better meet the increasing demand for safety and quality testing, as well as custom research and development testing in China.

Alternative 'ribbon cutting' celebration, unmasking NSF name with blue sand.

The new lab will harness our state-of-the-art testing capabilities to provide local engineering, chemistry and microbiology industries with more comprehensive testing services. The lab continues to develop and evaluate test methods in addition to creating new test procedures.

Sol Yu, Managing Director in China, opened the ceremony, documenting NSF's growth in China since the opening of its first office in Shanghai in 2005. *"This new laboratory represents the strengthening of our relationship with China and we hope, the continuation of our success and growth here."*

Forthcoming Courses

Pharma Courses Planned From mid-November 2019 to mid-March 2020

Pharmaceutical GMP Audits and Self-Inspections
(A CQI and IRCA Certified Training GMP PQS Lead Auditor Course)
November 11 – 15, 2019 ǀ Amsterdam, Netherlands ǀ £3,040 excl. VAT

Pharmaceutical GMP
November 19 – 21, 2019 ǀ Amsterdam, Netherlands ǀ £2,110 excl. VAT

Medicinal Chemistry and Therapeutics
November 25 – 29, 2019 ǀ Brighton, UK ǀ £3,230 excl. VAT

Pharmaceutical Packaging
January 20 – 23, 2020 ǀ York, UK ǀ £2,960 excl. VAT

Pharmaceutical Formulation and Processing – Part 1
February 3 – 7, 2020 ǀ London, UK ǀ £3,330 excl. VAT

Advanced Therapy Medicinal Products
New course
February 20, 2020 ǀ Stansted, UK ǀ £830 excl. VAT

Pharmaceutical Formulation and Processing – Part 2
March 9 – 13, 2020 ǀ London, UK ǀ £3,330 excl. VAT

Pharmaceutical GMP Audits and Self-Inspections
NEW LOCATION — HELD AT NSF HEADQUARTERS!
(A CQI and IRCA Certified Training GMP PQS Lead Auditor Course)
March 16 – 20, 2020 ǀ Ann Arbor, U.S. ǀ $3,950.00

Pharmaceutical GMP
March 17 – 19, 2020 ǀ Amsterdam, Netherlands ǀ £2,170 excl. VAT

Pharmaceutical Legislation Update
March 17, 2020 ǀ Manchester, UK ǀ £830 excl. VAT

Regulatory Affairs for QA: Marketing Authorisations
March 18, 2020 ǀ Manchester, UK ǀ £730 excl. VAT

Regulatory Affairs for QA: Variations
March 19, 2020 ǀ Manchester, UK ǀ £730 excl. VAT

Pharmaceutical Legislation Update
March 19, 2020 ǀ Amsterdam, Netherlands ǀ £830 excl. VAT

For more information, email **pharmacourses@nsf.org** or visit **www.nsf.org/info/pharma-training**

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.

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.

Complimentary 2019 Webinars

19 NOVEMBER What are the Key Topics When Auditing a High-Speed Packaging Facility
by Lynne Byers

17 DECEMBER How to Resolve Conflict Within Multi-National Organizations so That Everyone Flourishes
by Martin Lush

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

Is there a particular subject you would like covered in our 2020 webinar series? Contact us with your ideas.

New Medical Devices eLearning

> **ISO 13485:2016 – International Medical Device QMS Standard** – This course provides in-depth instruction and expert clarification of ISO 13485:2016, the standard which serves as a basis for many medical device quality management system (QMS) regulations around the globe.

Our medical devices eLearning also includes new courses on the EU MDR and the IVDR. We also offer pharma eLearning which includes courses on SOP writing, the roles and responsibilities of a responsible person and much more.

Visit our website to see our range of eLearning.

PHARMA AND MEDICAL DEVICES EVENTS WHERE WE WILL BE EXHIBITING AND SPEAKING

November 2019 – January 2020

> **CPhI Worldwide**
November 5 – 7, 2019
Frankfurt, Germany

> **Bio Europe**
November 11 – 13, 2019
Hamburg, Germany

> **Medica**
November 18 – 21, 2019
Dusseldorf, Germany

> **Arab Health**
January 27 – 30, 2020
Dubai, UAE

NEW-SELF ASSESSMENT TOOL AVAILABLE IN NSF'S PHARMA APP

The ten question Investigation and CAPA system assessment will rapidly pinpoint areas for improvement. Try it and don't hesitate to contact us for guidance. Visit the self-assessment tools section of the NSF Pharma app.
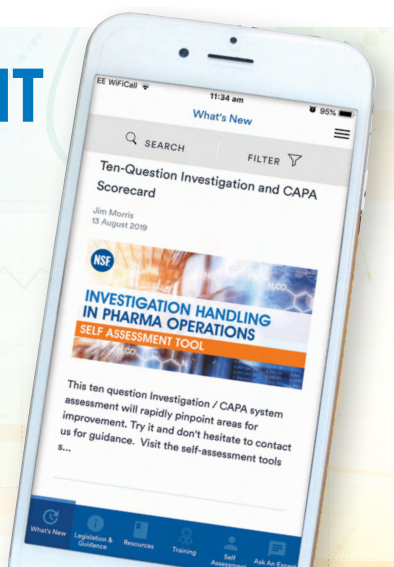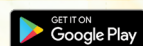
You can also access our training information and book courses while on the go!

Forthcoming Events & Webinars

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