

# Journal

2017, Issue 38

The right people. The right solution. The first time.™

## How Safe Are Your Products?

**EudraLex Vol IV Annex 1 Edition  
Manufacture of Sterile  
Medicinal Products**



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# welcome

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I started my career as a hospital medical microbiologist 38 years ago. One night a 16-year-old girl was rushed in with meningococcal meningitis. When we took a sample of spinal fluid I knew she was in trouble. Instead of being clear and colorless, it looked like soup. My Gram stain confirmed it was packed full of meningococcal bacteria. I left her at 4 a.m., in a coma, as the medics began the fight back with a barrage of IV antibiotics. Three days later I reported her fluid as clear and colorless and she left hospital four days later.

This edition focuses on her savior, pharmaceutical sterile products. When we manufacture them correctly, we save lives. When we get it wrong, the consequences can be catastrophic so, of course, it's no surprise they are heavily regulated! Our article on the proposed changes to EudraLex Annex 1 relating to sterile products on page 6 is a must read as is Maxine and Andy's article on FDA enforcement activities, see page 8. We recognize the importance of the Indian pharma manufacturing industry to global supply chains and, as a consequence, NSF has expanded its team to provide the world-class training and consultancy that is needed in this region, see page 20.

#### **Your final call to action:**

Make sure your patients are at the center of everything you do. Make sure everyone knows how your products impact the lives of others. As soon as companies allow patients to be forgotten, the unintended consequences can be dramatic for all concerned, whether you make sterile products or not.

Enjoy our Journal, keep in touch and best wishes.



Martin Lush



**Martin Lush,**  
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# Why Annex 1 is Important to You



by John Johnson,  
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Regardless of the dosage form you supply to market, whenever there is a revision to the EudraLex Volume IV GMP regulations, it is important to take in the wider picture. And with the introduction of a significant revision to Annex 1: Manufacture of Sterile Medicinal Products license holders and pharma suppliers should ask themselves:

- > Why is the regulation being changed?
- > How will it affect my operation or the company as a whole?
- > Does the revision give a signal to a change in perspective within EMA?
- > Does the revision give some clues on how the changes will be monitored and enforced?
- > What do I need to do to keep in-step with these changes, regardless of the dosage form I work within?

Failing to ask these questions, and failing to take the time to find the answers specific to your organization, is like driving in the dark at breakneck speed without your headlamps on.

Whilst Annex 1 is focused on sterile production, the proposed clarifications and the changes to be made will have a definite knock-on impact on how the regulators regulate and how the industry designs, operates and checks the effectiveness of the whole Pharmaceutical Quality System (PQS).

It is therefore important to examine the reasons for the revision to Annex 1 and ask yourself some key questions:

Key reasons for revision to Annex 1	What should I be asking myself, regardless of the dosage form I am responsible for?
1. New technologies mean that new regulations are required to clarify the GMPs. This is the first revision since Annex 1's inception in 1996.	- Does my organization utilize production, facility or QC technology that is unique or innovative? How would I present the scientific justification for that technology? How does it work? What happens when it doesn't work? How could I check its ability to ensure critical product quality attributes are met now and for the long-term?
2. The EU competent authorities are concerned about the pressures within the PQS – especially regarding a perception of higher staff turnover, heightened commercial pressures and projects that run late or are out of control. This means the authorities believe clearer regulations will help industry improve GMP compliance.	- Does my staff turnover within the critical position holder group exceed 15 percent per year? Am I losing my best people to other employers? How should I retain the high performers?  - How well does my organization introduce new products? Do we only introduce materials and drug products appropriate to the facility and the quality system currently in place?

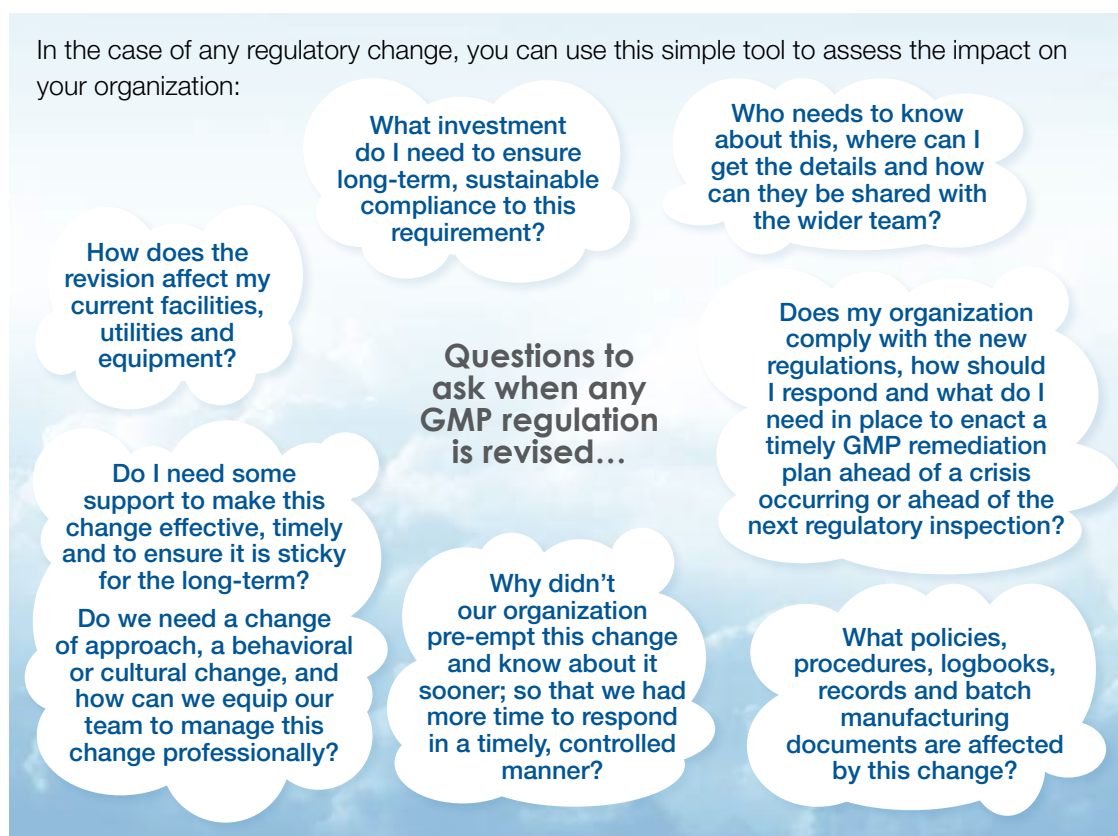


Key reasons for revision to Annex 1	What should I be asking myself, regardless of the dosage form I am responsible for?
<p>3. The authorities' unique view of the industry is troubling them. They are seeing recurring GMP deficiencies, basic defaults against the regulations, inadequate root cause analysis and ineffective CAPA. They are seeing poor deployment of ICH Q9 Quality Risk Management and issues concerning sterility assurance are not diminishing, causing recalls and product shortages. In short, when trust is eroded, there is a greater need for verification and enforcement.</p>	<ul style="list-style-type: none"> <li>- Does my PQS have a clear risk management process that leads to a risk register, acted on via quality objectives year after year?</li> <li>- Does my product impact assessment process tend to justify unsound, unscientific or bad practice, often just to seek a way of continuing to supply product without addressing the root causes?</li> <li>- Am I noticing recurring issues? Am I visually active in seeking transformational change in the severity and frequency of recurrence?</li> </ul>
<p>4. The authorities have noted a trend in fragmentation of supply chains leading to the diffusion of QA oversight and responsibility. Sterile products are often made in locations and by companies without a long-compliance history in this field with low level understanding of the technologies and risks. This is evidenced by the prevalence of basic GMP deficiencies noted on-site during regulatory inspections. As a consequence, Annex 1 needed to be made less ambiguous with less room for interpretation.</p>	<ul style="list-style-type: none"> <li>- How do my EU Qualified Persons oversee the supply chain as required by Annex 16, and how is this documented?</li> <li>- How well does my vendor approval system work and do I have any special cases where a person-in-plant is needed to guide, mentor and verify the performance of our contractor?</li> <li>- Do my manufacturing partners operate a quality system that meets ICH Q10 and is clearly used in day-to-day operations?</li> </ul>
<p>5. After the global recession 10 years ago, many firms slashed their training budgets and downsized the way they educate their staff and develop their managers. It is now evident that some critical position holders may have the "know-how" but not the "know-why". Hence the trend in sterile inspections for poor decision making, inadequately completed investigation reports and acceptance of repeat, low level issues – often first noticed during the regulatory inspection. More detail is needed in Annex 1 to provide clearer guidance and direction.</p>	<ul style="list-style-type: none"> <li>- Of course we train our staff, but do we educate them so that they can make the right calls at the right time? Are our training programs developing the subject matter experts of the future?</li> <li>- Do we have a successor program, do we define "station manning" to allow people to shadow managers, internal audits and key meetings so that they learn the role as part of their daily job?</li> <li>- How do we check that the training has been absorbed and best practice is implemented?</li> <li>- How do we deal with those who just don't get it?</li> </ul>





In the case of any regulatory change, you can use this simple tool to assess the impact on your organization:



### For more information:

- > Read the Tech Talk article on page 6 about the key anticipated changes to Annex 1
- > Visit our resource library ([www.nsf.org/info/pblibrary](http://www.nsf.org/info/pblibrary)) and watch the webinar EudraLex Vol IV Annex 1 – How Will It Affect You
- > Whether you are a steriles manufacturer or not, take some time to formulate a plan of action because, subtly but surely, your EU regulator is telling you:
  - Better regulation is needed as many sectors of the industry are clearly struggling to comply with the basic requirements of GMP
  - Product shortages, recalls and regulatory censure are very troubling to the authorities, and demonstrate that changes across the industry in the last 10-15 years are not visibly improving the quality or safety of products manufactured or supplied in and to global markets
  - Recurring GMP deviations and deficiencies against the GMP regulations demonstrate a lack of effective root cause analysis, a lack of rigor in identifying the right CAPA and an acceptance of variation that can lead to significant impact on product quality
  - Though a quality system (underpinned by a robust staff education program) is a mandatory requirement, it will **not deliver** the required level of quality assurance without the engagement of staff at all levels. This engagement is needed before the right communications, behaviors, culture and mindset can be put in place. The regulators are noting elegant quality systems across our industry but likewise they see products of variable quality and often made to inconsistent or inappropriate levels of GMP

We should all be asking ourselves... **WHY IS THAT?**





by John Johnson,  
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# Tech Talk



## What is Likely to be in the New Annex 1?

At the time of going to press, there are no certainties on what will be in the revision of Annex 1 of EudraLex Volume IV but our research has focused on:

> What the headlines are in terms of

- Clarification
- New expectations
- Corrections
- Areas that required or will require further discussion

> What effect this will have on the pharma industry

- For steriles manufacturing companies
- For other dosage form manufacturers

As covered in Journal 37's Summary of Anticipated Changes to Annex 1 article ([www.nsf.org/newsroom\\_pdf/pb\\_annex\\_1\\_eu\\_gmp\\_vol\\_iv.pdf](http://www.nsf.org/newsroom_pdf/pb_annex_1_eu_gmp_vol_iv.pdf)), the draft concept paper was issued by MHRA to the EMA Inspection Working Group (EMA IWG) in September 2014 and was worked on by an EMA team (rapporteur: Andy Hopkins MHRA) leading to submission of a full draft to EMA IWG in mid-2016. A paper will be published in April or May 2017 (during publication of this edition of the Journal).

These are likely to be the key revisions:

Section	Notes
1. Scope	Provides better linkage to other related parts of GMP such as 2003/94 Article 5, 2001/83 Article 23, Chapter 3: Premises and Equipment and Chapter 5.10 on protection from microbial and other contamination
2. Principles	Reinforces existing GMP requirements and removes ambiguity
3. General	Corrects some existing contradictions
4. Pharmaceutical Quality System	Major re-emphasis on the need for proactive and thorough implementation of quality risk management (with reference to ICH Q9), availability of documented evidence of compliance to ICH Q9 and adoption of the key risk management tools across the sterile production process  Underscores the need for a demonstrably timely, thorough and scientifically derived failure investigation process that includes a credible and justifiable product impact assessment  Key message: Risk assessment cannot be used to justify bad practice, especially in the aseptic core
5. Personnel	Mandatory requirement for goggles in the critical zones  Need to assess, train and enforce the right staff behaviors through initial and continued education programs  Need to define, train, assess, enforce and continually verify the correct aseptic technique
6. Premises	Implementation of ISO 14644; definition of cleanrooms and their environment  Reinforces the need for real-time trending, definition of out-of-trend and timely response to alarms  Clarifies the need for monitoring 5 µm particles in cleanrooms

7. Equipment	Guidance on the need for separation of process from operators and other sources of contamination; special requirements for restricted access barriers (RABs) and isolators
8. Utilities	Adoption of common controls and monitors for compressed air and water systems Special considerations for the prevention and removal of biofilms in water systems Generation of WFI will align with the European Pharmacopoeia (the use of reverse osmosis to produce WFI is permitted)
9. Production	Two areas required a lot of discussion (see below) Special considerations for small batch production, ATMPs, 'specials' and other technologies such as blow-fill-seal
10. Monitoring	Adoption and reference to rapid microbial identification technology Clarification on the design and interpretation of process simulation trials Clarification of what continuous monitoring of cleanrooms means, both for viable and non-viable monitoring methods Need for a documented risk assessment when deriving an environmental monitoring program
11. Quality Control	No significant changes expected
12. Glossary	Now included

The key areas requiring a lot of discussion were:

### Section 9. Production – Pre-Use Post-Sterilization Integrity Testing (PUPSIT)

Industry had long argued that PUPSIT has a theoretical or exceptional risk of damaging filters immediately before use or could contaminate the filter media, and that the act of sterilization of the filters has been proven not to affect the log reduction value that filters are expected to exhibit. As such, in some quarters, PUPSIT had been eliminated from the process with supplier certification and/or pre-use, pre-sterilization integrity testing being relied on. In other quarters, the opposite had been argued with no accepted justification for removing this critical filter integrity test (performed immediately before use). It is expected that PUPSIT will prevail and scientific justifications for alternatives may be challenged at regulatory inspection.

### Section 9. Production – Integrity Testing of the Final Drug Product

As technology has improved, 100 percent container closure integrity has become a compelling method for improving product quality, but the technology doesn't work reliably for all container/closure types yet. Offline sampling and testing (for example dye bath testing) or 100 percent inspection for gross container defects is still prevalent (with many companies also using bacterial challenge tests or leak rate testing during initial and periodic validation studies). However, regulators and industry want to see technology developed that would make 100 percent online container integrity testing possible and economically viable. Until there is a breakthrough in the technology that sees all container types capable of being tested online, it looks like offline, periodic testing for container closure integrity is here to stay.

### So, what happens next?

- > Adoption of the new annex is expected by end of 2017 and will be enforceable at some stage afterwards
- > Keep up-to-date with the changes via our webinars; view our 2017 schedule at [www.nsf.org/info/pharma-webinars](http://www.nsf.org/info/pharma-webinars) or watch our pre-recorded webinars in our pharma biotech resource library at [www.nsf.org/info/pblibrary](http://www.nsf.org/info/pblibrary)



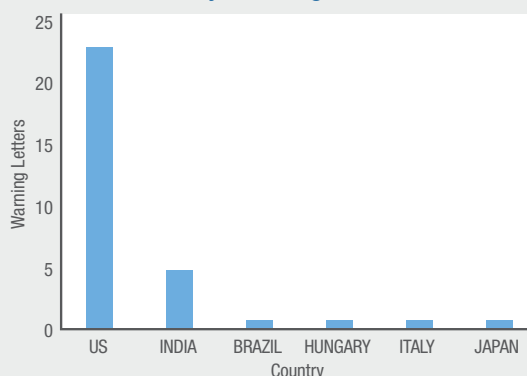
by Maxine Fritz,  
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# Heightened FDA Enforcement for Sterility Issues

We will never forget the tragedy that unfolded in 2012. An outbreak of fungal meningitis was traced to the New England Compounding Center and sickened over 800 people with 64 fatalities. This led to the passage in 2013 of the Drug Quality and Security Act, which gave greater authority to the U.S. FDA to regulate compounding pharmacies. As a consequence, since January 2015, 15 compounding pharmacies have received warning letters for significant violations of CFR 211 regulations relating to sterility control.

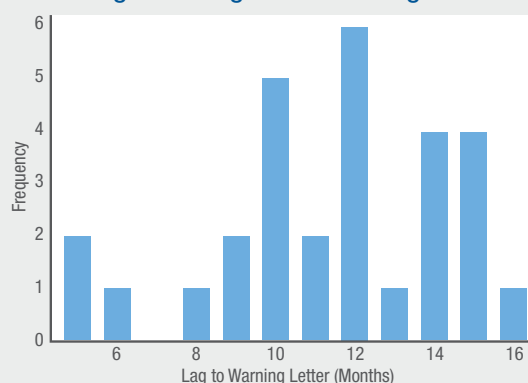
No doubt some of the compounders were caught off guard when they realized they are now subject to the regulations in 21 CFR Parts 210 and 211 and were hit with warning letters. The last thing we want at NSF is for our pharma customers to be subject to regulatory action or risk patient health, so we analyzed all of the warning letters issued to pharma and biologic manufacturers for sterility issues since 2015. Our analysis covers hundreds of pages of detail from 32 warning letters. Based on these findings, we would encourage you to review your quality systems and process controls and consider whether you need to shift or increase your efforts to close your compliance gaps. And remember, we are here to help.

**Sterility: Warning Letters**



This chart shows the number of warning letters issued over the past two years by country. The United States tops the list with 23 warning letters, but 15 of those are for compounding pharmacies. Overseas manufacturers can expect the enforcement “wave” to hit soon. Since October 2016, four of the last six warning letters were issued to foreign manufacturers, and two of those sites were also given import alerts.

**Histogram of Lag: 483 to Warning Letter**



This chart shows how long it usually takes for a FDA 483 to turn into a warning letter. (Full disclosure: Three warning letters had very long delays of two years due to special circumstances, so they were excluded from the chart.) Most facilities can expect at least eight to ten months allowance to resolve issues. But be careful! If the FDA is not satisfied that you are making progress, the warning letter may come much sooner.

Compounders are hit with slightly more sterility-related citations than traditional pharma plants (4.1 versus 3.7, respectively), but the difference is not statistically significant. This is a good indication that we can lump all the findings together to see what the FDA looks for during inspections.



Citation	Description	Count	% of WLs	Cum %
211.113	Control of Microbial Contamination	31	97%	25%
211.42c	Controls to Prevent Contamination	25	78%	45%
211.192	Investigations	15	47%	57%
211.28a	Gowning	12	38%	66%
211.160	Stability Testing	7	22%	72%
211.160	Laboratory Controls	7	22%	78%
211.68b	Data Access/Control/Integrity	6	19%	82%
211.167	Test each Batch for Sterility/Particulates	6	19%	87%
211.194	Laboratory Records	5	16%	91%
211.67	Equipment Cleaning	5	16%	95%
211.63	Equipment Design	2	6%	97%
211.58	Equipment Maintenance	1	3%	98%
211.110	In-Process Testing	1	3%	98%
211.165b	Release Testing	1	3%	99%
211.84(d)(6)	Component Testing	1	3%	100%



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The table above shows a summary of the regulations cited by the FDA. From the top row, we see that 31 out of 32 (97 percent) warning letters cited regulation 211.113, Control of Microbial Contamination. There were 125 citations in total, so 211.113 accounts for 25 percent of all the citations. **If users focus on the top half of the table (seven citations) they will cover over 80 percent of the observations cited in the warning letters.**

We recommend that you focus your initial efforts on the “vital few.” Pay particular attention to these items in management reviews. Conduct special internal audits and monitor non-conformances to create metrics around these regulations and trend performance over time. See Journal Issue 35 for more advice on KPIs and tracking quality metrics. Once these systems are in control, you can move on to other items in the table.

Here are a few items that have tripped up other manufacturers:

- > Not incubating rejected (integral) vials during media fills
- > Inadequate smoke studies that do not show the effects of interventions
- > Inadequate rationale or inappropriate location of settle plates and NVP probes
- > Ineffective cleaning agents or methods (repeated contamination incidents)
- > Not identifying contaminants (even if triggered by alert limits rather than action limits)
- > Partial release of a batch with incomplete investigation and inadequate justification

There are so many more incidents and practices that jeopardize sterility assurance. The FDA now routinely advises manufacturers to engage a third-party cGMP consultant to conduct an assessment of the sterility assurance program. NSF has industry-leading experts in environmental monitoring, sampling, aseptic processes, investigations and much more. We can help with identification and remediation.

For any questions and should you need assistance, please contact us at **[mfritz@nsf.org](mailto:mfritz@nsf.org)** or **+1-202-828-1585**.



by John Johnson,  
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## Essential Rules when Investigating GMP Deviations during Sterile Processing

At the heart of what we do in industry, **we are problem solvers!** This is never more acute than in the field of sterile manufacturing.

Is there a more challenging production process on earth than one which:

- > Makes a product that is injected directly into the bloodstream, bypassing almost all of the body's natural defense mechanisms
- > Makes a product that, by virtue of its administration, has an almost immediate effect with little chance of turning off or countering its action
- > Can be infused or injected into tiny neo-nates, geriatrics, the terminally ill and patients who are immunocompromised, vulnerable or wracked in pain

Our objective in everything we do has to come down to one overriding priority and that is **patient safety**.

This sentiment is often portrayed on company websites and posters, but how often do we remind ourselves and our team that the decisions we make on a daily basis make a huge difference to patient health and wellbeing?

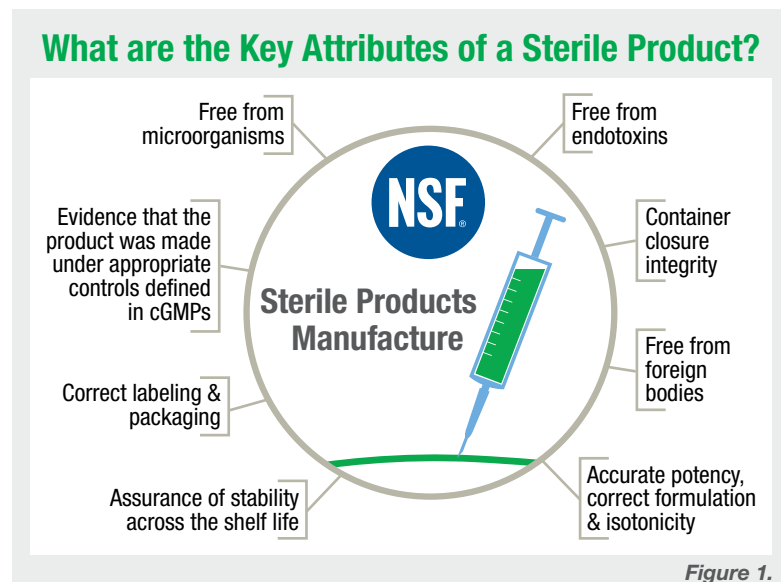
Even writing about this experience brings up the hairs on the back of my neck. Many years ago I was the EU Qualified Person and Quality Director at a large aseptic facility producing parenteral nutrition products in large volume bags, directly infused into patients who could no longer eat and were often very ill. It was a fast moving business, operating within very short lead times from order to supply (often less than 24 hours), supplying homes and hospitals in a 300-mile radius of the facility. Each formulation was customized to the patient and formulated aseptically in laminar flow cabinets and subject to sterile filtration. I will never forget one particular day. I decided to follow the supply chain from warehouse to cleanroom to patient and actually go to the patient's home where our driver would deliver the sterile infusion bag. As I met the frail old lady and watched her nurse attach the bag I made and QP released that morning, and watched that precious liquid roll down the tubing into the back of her hand, I felt a deep upwelling of responsibility. What if we had made a mistake? What if I missed something? What if the product was contaminated or contained the wrong ingredients? What if...? Somehow she sensed this unease, grabbed my arm with a grip that belied her size, fixed me in a watery gaze and said to me, "I saw your name on the label, Mr. Johnson. It is going to be OK, isn't it?" I will never forget that moment.

How do we **know** it's going to be OK? Not just know, but **be sure** it's OK?

This is where our quality system, our people, our facilities, our science and our staff behaviors make the difference. Of course we must continue to seek better ways of identifying and mitigating risk through good design of facilities, records and procedures and through effective controls and monitoring. We seek to identify and eliminate risk through effective process development, validation and continued process development – always seeking clear links between the process, the instructions, the records and the assurance of the key quality attributes of sterile products. See *Figure 1*.

It's always a great idea to check that every policy, procedure, instruction, record, validation protocol or log is designed to assure at least one of these attributes and that none of these attributes are left to chance. Next time you review a batch record or perform an audit of a steriles facility, see if you can find the key steps the organization takes to assure each of these attributes. Can you find them, do they work and how do you know?

Always remember that making sterile products is dependent on a multitude of details that are dependent on effective design, good controls and stringent monitoring. When Sir David Brailsford set out to transform the success of the Great Britain Olympic cycling team, he knew that there was no silver bullet for success and that almost imperceptible improvements across an infinite



number of controls would be the way to dominate the sport. In the same way, making sterile products demands an attention to detail across all disciplines and a passion to flawlessly execute processes each and every time. More than that, it requires us to continually examine the pressures and risks in the process and eliminate those fleeting undetected issues that can lead to product contamination and patient harm.

But in the real world, things go wrong and we are employed to detect these issues and eliminate them from the supply chain so that patients are not put at risk. Equally we are employed to supply products to meet patient needs, so we cannot just reject batches and interrupt the supply chain whenever a variation exists.

So what are the best practices in dealing with variation?

Having a uniquely broad view of the industry's processes for dealing with variation, we can see that most organizations fall into three categories:

- > Little variation or risk seen; they are not looking for improvement (this is a time bomb)
- > Variation and risk seen; superficial investigation leading to recurring issues
- > Overly complex, overdesigned processes; can't see the true concerns due to the noise and complexity in the system

If every time you ate your breakfast, Big Brother compelled you to read the cereal packet line by line, very quickly you would ignore the instruction, try to follow it but do it differently every time or pretend you had read it when you hadn't! Isn't this a similar situation to when we present our teams with 50-page SOPs, unfollowable instructions and overly complex processes?

### The key message here is:

- > Especially in steriles manufacturing, staff have to be educated in the risks, science and behaviors, not just trained in operating equipment
- > SOPs and records must be clear, unambiguous and error-proofed, designed with and by the users themselves

When things go wrong, there are five key non-negotiables that should be defined on the front page of your deviation investigation SOP. There are of course other key requirements but without any one of these, it is inevitable that the wrong conclusions will be made, inaccurate root causes will be found and, costly time-consuming CAPA will be defined; without a hope of preventing a recurrence.



Here are the “five to thrive” in terms of investigating GMP deviations or deficiencies:

FIVE TO THRIVE		
Key process	Measure or evidence	How could this be used in a deviation associated with sterile processing?
Immediate engagement	All issues are logged and triaged within one shift, evidenced by real-time logging.	An issue occurs. Staff members are trained to notice it. They don't pass it by. They are educated to be alert to the problem. They log it and know how to escalate the problem as their training was based on case studies. The investigation begins immediately before the trail goes cold.
Gemba	A “crash team” is engaged to go to the place of the issue and support its resolution.	A team of respected subject matter experts is available to support the operational team when exceptional events occur. They are highly expert, open minded and well drilled. In sterile processing, this may include expertise in microbiology, cleanrooms, sterilization, disinfection, gowning and aseptic behaviors.
Triaging using a documented risk assessment	A pro forma is used to assess risk, completed at the time of the gemba within one shift of the occurrence.	The pro forma is used to assess risk leading to an effective correction, e.g. terminating the aseptic fill operation immediately, continuing once measures are taken or recording as an observed risk. The right people are there to make this decision, accessing the right information and recording their assessment with scientific rigor.  In steriles manufacturing, it is impossible to make an accurate risk assessment from a meeting room, days after the event.
Klein process to determine potential root causes	Staff are trained in timely and thorough processes for investigation. Blame free culture allows investigations to be conducted accurately without recrimination.	Staff members use the five whys, Ishikawa, the six Ps, is/is not/ maybe, RAPID decision making, FMEA, etc. to bring the issue to the surface. They are trained in sensitive, open-minded, blame-free investigations where words and actions are critical to transparency and objectivity. In steriles manufacturing, a holistic approach to how sterility is assured is critical and will depend on a multidisciplinary approach by staff who work well together to piece together the chain of events that led to the risk.
Document in real time using an investigation worksheet	Investigations are completed at a rate dependent on their risk; the 30-day, one-size-fits-all expectation isn't often appropriate to high-risk events.	The pro forma is used as a trigger to ensure the right risk-based decision making tool is used for each situation. It also records any observations and immediate corrections (“make safe”). The tools (from ICH Q9 and NSF best practices) are used to structure the investigation and ensure no evidence is missed at the time. The pro forma is the first part of the deviation investigation report and records the product impact assessment, assessment of risk to the facility and any impacts on the product quality attributes. It also records the facts and decisions made during the investigation.  In steriles manufacturing, it is often impossible to identify the right course of action from a meeting room, days after the event. Investigations need to be thorough and timely; not hampered by a lack of resources.

### For more information:

- > NSF's BITE toolkit is helping firms cut through the weeds and define some basic unalienable rules for the quality system – visit our website to see the brochure: [www.nsf.org/info/bitetoolkit](http://www.nsf.org/info/bitetoolkit)
- > View our complete 2017 training schedule including the courses Human Error Prevention and A-Z of Sterile Products Manufacture: [www.nsf.org/info/pharma-training](http://www.nsf.org/info/pharma-training)
- > Visit our resource library and watch Martin Lush's webinar on the art and science of simplification – [www.nsf.org/newsroom/webinar-the-art-and-science-of-simplification-how-to-win-your-war-on-c](http://www.nsf.org/newsroom/webinar-the-art-and-science-of-simplification-how-to-win-your-war-on-c). You will also find other useful videos, white papers and case studies: [www.nsf.org/info/pblibrary](http://www.nsf.org/info/pblibrary)



# New EU Medical Device Regulation Adopted April 5, 2017

## NSF Industry Forum Already Examined Impacts

The year 2017 brings significant changes to the regulatory landscape across Europe, following the publication of the new European Medical Device Regulation (MDR) and In Vitro Diagnostics Regulation (IVDR). To prepare for the coming changes, NSF International hosted an industry forum in the UK on November 30, 2016, to explore the likely impacts on company planning, finance and human resources.

### Setting the Scene

More than 30 regulatory professionals from a wide range of medical device companies attended the forum. James Pink, VP for NSF Health Sciences Medical Devices provided an overview of the regulations. After the PIP implant scandal and the clinical data inadequacies associated with metal-on-metal resurfacing of implants, it became apparent that changes were required in the medical device directives and the regulation.

The new regulations were proposed by the European Commission in February 2012, and the European Parliament voted on April 5, 2017, to adopt them. The industry is now subject to a three-year transition period for medical devices and a five-year period for in vitro diagnostic products (IVDs). Thereafter, compliance will be monitored by unannounced audits.

Notified bodies have also been significantly affected by increased scrutiny, which has caused loss of designation or withdrawal. This has greatly impacted manufacturers that have lost their notified body or have experienced delays in the issue of CE certificates. Manufacturers will be further impacted by changes in product classification, which may trigger portfolio reviews, and by the introduction of new, additional scrutiny that can make new product introductions more difficult due to indeterminate timescales and costs.

Addressing all of these impacts requires careful business planning. Plans might include recruiting additional qualified staff to help manage the transition, ensuring that the organization has comprehensive

clinical and technical data for their product families, being well prepared for audits, and reviewing the arrangements for post-market surveillance.

### Implications for IVDs

The new regulations that apply to IVDs, also published in April 2017, and a full description of the changes will appear on our website [www.nsf.org/info/eumdr](http://www.nsf.org/info/eumdr)



### Industry Impact

To gauge the likely effect of the changes on the industry, NSF used an electronic voting system to gather feedback from the attendees regarding several different areas of impact. In the first voting session, delegates were asked about the likely impact on human resources, training and company finances, and about which changes will have the greatest influence on strategic goals.

In the second voting session, NSF asked delegates to provide feedback on various aspects of how they are planning to introduce the new regulations. Focus areas were internal communication, the need for external advice, access to notified bodies and the impact of Brexit.



Visit our website [www.nsf.org/info/eumdr](http://www.nsf.org/info/eumdr) for the full article and to see the complete results from the day's proceedings.



by Howard Broadbridge, Business Development Manager, NSF Health Sciences Medical Devices



by Maxine Fritz,  
Executive Vice  
President, NSF  
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Consulting

# Points to Consider when Auditing a Terminally Sterilized Drug Product

There are two broad methods to produce a sterile drug product, terminal sterilization and aseptic processing. There are various methods of terminal sterilization including moist heat sterilization, dry heat/depyrogenation, irradiation and ethylene oxide. Terminal sterilization is always the preferred method over aseptic processing when possible. However there are situations when terminal sterilization cannot be performed and one must rely on aseptic processing. Aseptic processing does present a higher risk of microbial contamination of product than terminal sterilization. When conducting an audit of the terminally sterilized product process, consider the following factors.

## Facility and the Environment

- ☐ Has the firm performed a risk assessment of its facility and equipment?
- ☐ Does the firm understand the areas of risk as they relate to contamination of drug product?
- ☐ Are the facility, the equipment layout and the air handling system designed and suitable for preventing viable and non-viable contamination?
- ☐ Is the material and personnel flow unidirectional (dirty to clean)?
- ☐ Is there trend data to demonstrate the cleanroom quality?
- ☐ Does the facility have smooth cleanable surfaces? Are the materials non-porous?

## Support Utilities

Water systems, in particular the WFI generation equipment and the distribution loops, need careful review.

- ☐ Are there detailed P&IDs/as-built diagrams?
- ☐ Is there a risk assessment that includes slopes, dead legs, non-sanitary fittings and leaks?
- ☐ Is there appropriate sampling at the points of use?
- ☐ Is there inline monitoring for TOC and conductivity?
- ☐ Is there trend data for chemistry, microbiological and endotoxin tests?
- ☐ Are appropriate alert and action levels established?
- ☐ Is there a scheduled sanitization?
- ☐ Is passivation performed when needed and what material is used to passivate?

Air handling units and high efficiency particulate air (HEPA) filters are important to maintain airflow, air filtration and overall air quality.

- ☐ Is the facility controlled and classified?
  - ☐ Are the HEPA filters integrity tested?
  - ☐ Does the testing include air velocity measurement?
  - ☐ Are there appropriate pressure differentials, and temperature and humidity set points?
  - ☐ Have airflow pattern (smoke) studies been conducted under dynamic conditions to verify the unidirectional airflow and air turbulence within the critical area where sterilized drug product, containers and closures are exposed to environmental conditions?
- 

## Terminal Sterilization Validation and Qualification

- ☐ First and foremost have all the sterilization processes been validated and is all the equipment such as autoclaves and ovens been qualified?
  - ☐ What type of sterilization cycles were used, for example was it bioburden based or an overkill?
  - ☐ Does the validation documentation describe the equipment and include the IQ/OQ/PQ data?
  - ☐ Are there procedures for revalidation? What is the time period and is it based on risk?
  - ☐ Does the validation documentation include empty chamber and loaded chamber heat distribution studies?
  - ☐ Was there an identified worst case load?
  - ☐ Were Biological Indicators (BIs) used to validate the cycles?
  - ☐ What type of indicator was used?
  - ☐ What organism was used (genus and species) and is it appropriate for the type of sterilization?
  - ☐ Is there a verifiable spore count and what is the approximate D-value of the BI?
  - ☐ How many BIs were used per sterilization load?
  - ☐ Are there any worst case locations and were the BIs placed in these locations?
  - ☐ Is there a diagram of the distribution of the BIs in the loading pattern used?
- 

Please note there are many other considerations when auditing a terminally sterilized drug product and many other issues to consider for an aseptically processed drug product that are not covered above, including having a solid PQS, which we will discuss in our next Journal.

If you need assistance or have questions, please contact me at [mfritz@nsf.org](mailto:mfritz@nsf.org) or at **+1-202-828-1585**.

# Regulatory Update



by Pete Gough,  
Executive Director,  
NSF Health  
Sciences Pharma  
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## EU News

### GMP Legislative Changes

In January 2017, the European Commission published a draft GMP regulation for IMPs and a draft GMP directive for marketed products, together with annexes that provide a cross-reference between the articles of the current GMP Directive 2003/94/EC and the new drafts. The drafts had a very short consultation period of just under one month and unfortunately went virtually unnoticed as they were published on a new EC portal for consultations, not on the usual commission web pages where these kinds of consultations have previously been announced.

The draft directive for marketed products is essentially the same as Directive 2003/94/EC but with all references to IMPs removed.

The draft IMP GMP regulation addresses the missing QP checks that are in Directive 2001/20/EC, but are not in the new Regulation 536/2014, in that it requires:

- > Imported product to be made in accordance with GMP equivalent to EU GMP for IMPs
- > Manufacturing to be compliant with the clinical trial authorization
- > QC testing to be performed and the results to conform to the product specification file
- > Certification to be recorded in a register or equivalent document

The draft IMP GMP regulation also includes arrangements for GMP inspections of IMP manufacture in Articles 17 to 25.

### Implementation of Health-Based Exposure Limits

Chapters 3 and 5 and Annex 15 of the EU GMP guide were updated in 2015 to include the requirement that the need for dedicated facilities and the establishment of cleaning validation limits should be based on a toxicological assessment that establishes a permitted daily exposure (PDE) for the active ingredient(s). To support this change the EMA published

guidance on setting health-based exposure limits (HBELs) that became effective in June 2015.

In January 2017 the EMA published a draft Q&A document with 14 questions and answers regarding the implementation of HBELs. The document is supposed to clarify requirements but seems just as likely to cause further confusion.

This new Q&A document introduces the concept of “highly hazardous” products and active substances, which are identified based on their inherent toxicological and pharmacological characteristics.

Q4 and Q6 indicate that for products not regarded as highly hazardous the traditional process of calculating safe limits based on 1/1000th of the therapeutic dose can continue to be used for new and existing products and for non-highly hazardous products these can be regarded as HBELs.

Q6 states that although the EMA guideline on setting HBELs (EMA/CHMP/CVMP/SWP/169430/2012) may be used to justify cleaning limits, it is not intended to be used to set cleaning limits at the level of the calculated HBEL. The cleaning limits should continue to be based on risk assessment **and additional safety margins** to help account for uncertainty in the cleaning processes and analytical variability.

At their symposia in London in December 2016, the MHRA stated that the interpretation of EU inspectorates of this answer to Q6, is that cleaning limits will not likely be relaxed from limits established and validated prior to the 2015 GMP updates. This is contrary to the more pragmatic view previously advised by MHRA but is being imposed by the EMA to drive consistency across Member States.

What is not currently clear is whether companies that have invested significant time and resources to establish PDEs and modify their cleaning validation limits accordingly now have to revert to their previous limits in instances where the health-based limits are higher than those based on the previous unscientific, arbitrary limit of 1/1000th of a therapeutic dose.





## U.S. News

### Office of Regulatory Affairs – Program Alignment Group Initiative

The Office of Regional Affairs (ORA), which manages FDA's 5,000 field inspectors, plans to make its Program Alignment Group (PAG) initiative operational by May 15, 2017. The aim is to complete this major reorganization of the FDA field force in fiscal year 2017.

This change will see the establishment of specialized groups of field inspectors for drugs, biologics, medical devices, food, etc. The ORA will maintain 20 district offices across the U.S., some concentrating on certain product areas, such as food or drugs, with additional specialists covering other areas.

The ORA now has senior-level program directors at FDA headquarters who oversee operations for six main product areas: food, biologics, drugs, medical devices, bioresearch monitoring and tobacco. Each district office will have a director, plus program managers to head inspection cadres at that location.

### FDA Final Guidance on Current Good Manufacturing Practice Requirements for Combination Products

The final version of this guidance was issued in January 2017, two years after the draft was issued. The final version does not contain any significant changes compared with the draft, but was expanded by 13 pages, 62 footnotes, a new chapter (glossary) and several new passages and amendments. The guidance has also been enhanced with many helpful examples.

The guidance gives combination product manufacturers two options for GMP compliance: satisfy all drug GMPs and independently all device quality system (QS) requirements, or implement a streamlined QS that is based on one primary QS (e.g. drug, device or biologic)



by Andrew Papas,  
Vice President  
of Regulatory  
Affairs, NSF Health  
Sciences Pharma  
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Obviously, patients have to be protected from cross-contamination so this issue is a very important part of GMP. It is regrettable that less than two years after HBELs were introduced into EU GMP these clarifications have to be made. It would have been better to ensure that the 2015 revisions of the GMP guide more clearly stated the expectations for HBELs so that companies had a clear picture of what they needed to do to comply before they made significant investments.

### EU-U.S. Mutual Recognition Agreement

In March 2017, the European Union (EU) and the United States (U.S.) signed a mutual recognition agreement (MRA) for inspections of manufacturing sites for human medicines conducted in their respective territories. This MRA means that EU and U.S. regulatory authorities will be able to rely on each other's information as regards to facilities in the EU or U.S. that manufacture medicines and active pharmaceutical ingredients for the European and American markets.

The agreement is an annex to the EU-U.S. MRA which was signed in 1998 but was not implemented. The provisions of this MRA annex become effective in a phased manner:

- > The mutual recognition of inspections will take effect on November 1, 2017, unless the FDA has not completed its assessment of at least eight EU Member State competent authorities, in which case, the MRA will become effective once the FDA has completed eight assessments
- > The provision that imports from the U.S. no longer need to be re-tested on importation into the EU will not apply until the FDA has completed its assessment of all EU Member States, which is scheduled for July 15, 2019

In its blog the FDA says it has committed to enter into a similar agreement with the UK post Brexit if necessary.

# Regulatory Update



and supplemented with specific provisions from the other QS to ensure compliance. Note the primary QS chosen by a company must be independent of the office that oversees the application. Helpful examples within the description of each 21 CFR Part 4 supplemental QS provision are provided.

The guidance also outlines how to develop a streamlined QS through three hypothetical combination product scenarios: a prefilled syringe, drug-coated mesh and drug-eluting stent.

Outside of this guidance, the 21st Century Cures Act signed into law by President Obama in December 2016 contains a number of initiatives, including a section on combination products that requires the FDA, within 18 months of the act going into effect, to identify and publish the types of combination products and manufacturing processes where GMP requirements may differ from the streamlined approach described above. It's unclear at this time what products or processes may be considered by FDA for alternative GMP requirements. We'll watch for signals from FDA in the upcoming year.

## ICH News

### Implementation of ICH Q3D

As the Q3D guideline focuses on elemental impurities there will be consequential changes to pharmacopoeia requirements. USP has announced that it will implement a new General Chapter <232> on Elemental Impurities Limits and delete General Chapter <231> Heavy Metals on January 1, 2018. In January 2017 the EDQM issued a paper describing how Q3D would be integrated into the European Pharmacopoeia. Supplement 9.3 will contain new general texts and methods with an implementation date of January 1, 2018.

### Draft Q11 Development and Manufacture of Drug Substances – Questions and Answers (Regarding the Selection and Justification of Starting Materials)

Since the ICH Q11 guideline was finalized in 2012, worldwide experience with implementation of the recommendations on the development and manufacture of drug substances has given rise to requests for clarification relating to the selection and justification of starting materials. This ICH guideline follows an earlier effort in the EU to further clarify some of the expectations arising from this section of Q11 in Sept 2014 (EMA/448443/2014). The issue being addressed is that the Q11 guideline, intentionally written at a high level, leaves the determination of the API starting material(s) open to interpretation by both the agencies and applicants.

The Q&A provides more insight on interpreting phrases such as: *“A starting material is incorporated as a significant structural fragment into the structure of the drug substance,”* *“impurities persist”* and *“substance manufacturing process should be described in the application.”* It also provides insight on the stage at which process steps should be included in CTD Section 3.2.S.2.2 Description of Manufacture Process and Process Controls, based on the Q11 risk assessment. The designation of the starting material(s) should be based on process knowledge for the intended commercial process. It is emphasized that all the general principles in ICH Q11 Section 5 should be considered holistically, together with the clarifications in the Q&A document, rather than applying a single general principle or Q&A clarification in isolation.

For legacy products approved before Q11, ICH indicates that previously defined API starting materials already accepted by regulatory authorities would not need to be re-justified against the ICH Q11 general principles or recommendations included in the Q&A document, unless significant changes are made to the manufacturing processes and controls.

# NSF News...



## NSF International's Bob Pietrowski Retires as Vice President of Global Health Sciences Division

We've recently made a few staff changes in the pharma biotech team.



NSF International has announced the retirement of Bob Pietrowski, Ph.D., a 40-year veteran of the pharmaceutical and medical device industries who has served as Vice President of NSF International's Global Health Sciences Division since 2013. Bob will truly be missed by everyone at NSF!

Martin Lush, who previously led our pharma biotech business, has been appointed Global Vice President of NSF Pharma Biotech Consulting and Medical Devices based in our office near York, UK.



For more information, visit our newsroom and read the press release: [www.nsf.org/newsroom](http://www.nsf.org/newsroom)



### Congratulations to Mike Halliday, John Johnson and Anne Davies



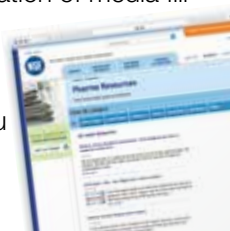
Based in the UK, Mike has been appointed Executive Vice President of NSF Health Sciences Pharma Biotech



Consulting and John has been promoted to Vice President. Anne Davies has also been appointed Associate Client Director.

### Answers to YOUR Problems in Just Six Minutes: "6-2-FIX in 6" Videos are Coming Soon

Some time ago we asked you about the challenges you face and the problems you wanted help in solving. We took your list and created a series of short, solution-packed videos, covering everything from how to change quality culture to the successful investigation of media fill failures. Six essential rules to fix your problem in just six minutes. We will let you know when these are available so watch out for a progress report.



### DOWNLOAD NSF'S PHARMA BIOTECH MUST-HAVE APP!



NSF International has launched its new pharma biotech app. The app is a must-have for any pharma biotech executive looking to:

- > Stay up-to-date on the latest industry regulations and news
- > Access a wealth of free resources to help you make better business decisions
- > Get a snapshot of your company's health with our self-assessment quizzes
- > Contact NSF experts to help with any business issues

**Stay connected – Download NSF's pharma app today. Visit the App Store or Google Play Store and search [NSF Pharma](#)**





## NSF in India...

### NSF Expands India Office to Develop Pharma Biotech Capabilities

NSF's office in New Delhi is being expanded to establish a local presence for pharma biotech regulatory and compliance-related training and consultation services. The office will expand NSF's pharma biotech services in India and establish long-term solutions to the business and GMP challenges that Indian companies face.



### NSF and IDMA Offer Pharmaceutical Quality Management Education in Bangalore

NSF is partnering with the Indian Drug Manufacturers' Association (IDMA) to offer a customized, five-module Pharmaceutical Quality Management (PQM) education program in Bangalore. Pharmaceutical industry professionals who complete this highly interactive MBA style, advanced education program will earn an internationally recognized certification in GMP compliance from NSF International and IDMA.

This unique, internationally recognized and independently assessed program has been

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.

The program begins in September 2017 and places are strictly limited to ensure quality and world-class education, so please book soon as there is a very high demand for places.

View our Advanced Program in Pharmaceutical Quality Management brochure or webinar for more information:

**[www.nsf.org/info/pblibrary](http://www.nsf.org/info/pblibrary)**



*Martin Lush and Maxine Fritz with IDMA Board Members, Government Officials and Industry representatives at the launch of the APPQM.*





## India Pharma Bangalore Shaping the Future of Indian Pharma

In February 2017, NSF's pharma biotech team consisting of Martin Lush, Maxine Fritz, Arpit Goel and Jyoti Bhasin attended India Pharma 2017 at the Bangalore International Exhibition Centre in Bengaluru.

The event covered the whole process of pharmaceutical manufacturing, from various kinds of manufacturing/processing machineries to lab equipment, analytical instruments, APIs and other total solutions.

Martin Lush participated in a panel discussion with international regulators on international harmonization. He also presented a session on NSF's Advanced Program in Pharmaceutical Quality Management. Maxine Fritz also participated in an expert panel on data integrity alongside FDA and U.S. experts.

Over 3,000 delegates and officials attended the three-day day event, emphasizing the leading role India will play in the development and manufacture of pharmaceuticals for many years to come.

## New Indian Associate – Sridhar Rao



To further expand NSF's capabilities in India, we are adding staff to our team.

Sridhar Rao has joined us as an Associate supporting our training and consultancy

activities in the Asia Pacific region. Sridhar is a trusted technical specialist with significant experience in pharmaceutical manufacturing and quality assurance covering oral and sterile dosage forms.

With a sound track record of accomplishments in a career spanning over 36 years, he has proven achievements in leading the quality unit for multi-locational sites which involve coordinating efforts with various cross-functional teams. Welcome to the NSF team!

## NSF Welcomes Mehul Patel to the Team



We would like to welcome Mehul Patel to the team as Director of Quality Systems in the U.S. Mehul is a pharma biotech professional with extensive

experience in the areas of domestic and international regulations, helping clients successfully remediate regulatory injunctions and notifications.

He has over 17 years' experience in the industry and is well versed in manufacturing and quality systems. His areas of expertise include cGMP, CFRs, ISO, ICH regulations applicable to drug product, drug substance manufacturing and validation, and OTC drug regulations.

## Martin Lush: Keynote Speaker at PDA Europe in Berlin, June 13-14, 2017

Martin will open this prestigious event with the presentation – The Political Landscape and the Future of the Pharmaceutical Industry. If you're interested in your future, listen in or find Martin at the NSF booth (13) for his insight and answers.

## Podcasts On-The-Go



To make your life easier, NSF now offers podcasts on some of our most popular white papers and case studies! To listen to our podcasts on vital topics including human error, data integrity, changing GMP behaviors, remediation, simplification and more, download our new pharma biotech app or visit our resource library today:

[www.nsf.org/info/pblibrary](http://www.nsf.org/info/pblibrary)

# Forthcoming Courses & Events

What's planned for June to November 2017 (Including our webinars)

## Effective and Efficient Process Validation: The Science and Risk-Based Approach

June 13-15, 2017

Manchester, UK

Course Fee: £2000 excl. VAT

## Pharmaceutical GMP

June 19-22, 2017

Manchester, UK

Course Fee: £2300 excl. VAT

## Techniques for Effective Failure Investigation for Sterile Products

June 19-22, 2017

York, UK

Course Fee: £2300 excl. VAT

## A-Z of Sterile Products Manufacture

June 26-30, 2017

Manchester, UK

Course Fee: £3000 excl. VAT



## Changing GM Behaviors

June 29-30, 2017

Manchester, UK

Course Fee: £1540 excl. VAT

## The Role and Professional Duties of the Qualified Person

July 17-20, 2017

York, UK

Course Fee: £2750 excl. VAT



## Mathematics and Statistics

September 11-14, 2017

York, UK

Course Fee: £2750 excl. VAT



## Human Error Prevention

September 13-15, 2017

Amsterdam, Netherlands

Course Fee: £2000 excl. VAT

## Pharmaceutical GMP Audits and Self-Inspections

(An IRCA Certified Pharmaceutical QMS Auditor/Lead Auditor Course)

September 18-22, 2017

York, UK

Course Fee: £2880 excl. VAT



## Techniques for Effective Failure Investigation

September 26-27, 2017

Manchester, UK

Course Fee: £1540 excl. VAT

## Good Distribution Practice

October 2-3, 2017

York, UK

Course Fee: £1540 excl. VAT

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

October 3, 2017

York, UK

Course Fee: £770 excl. VAT



## Good Clinical Practice

October 11, 2017

York, UK

Course Fee: £770 excl. VAT

## Pharmaceutical Law and Administration

October 16-20, 2017

York, UK

Course Fee: £3395 excl. VAT



For more information, email [pharmacourses@nsf.org](mailto:pharmacourses@nsf.org) or visit [www.nsf.org/info/pharma-training](http://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.



The right people. The right solution. The first time.™

## Free QP Seminar for Prospective QPs and Sponsors

October 17, 2017

York, UK

Course Fee: FREE

## Pharmaceutical GMP Audits and Self-Inspections

(An IRCA Certified Pharmaceutical QMS Auditor/Lead Auditor Course)

October 30 – November 3, 2017

Amsterdam, Netherlands

Course Fee: £2880 excl. VAT



## GMP for Clinical Trials Manufacture and Supply

November 6-9, 2017

Amsterdam, Netherlands

Course Fee: £2670 excl. VAT



## Analysis and Testing

November 13-17, 2017

York, UK

Course Fee: £3395 excl. VAT



## Pharmacovigilance

November 13, 2017

York, UK

Course Fee: £770 excl. VAT

## Pharmaceutical GMP

November 20-23, 2017

Amsterdam, Netherlands

Course Fee: £2300 excl. VAT

## A-Z of Sterile Products Manufacture

November 27 – December 1, 2017

Amsterdam, Netherlands

Course Fee: £3000 excl. VAT



## Internal Audit Training

November 30 – December 1, 2017

York, UK

Course Fee: £1540 excl. VAT

### EVENTS

### 2nd PDA (Parental Drug Association) Europe Annual Meeting

June 13-14, 2017

Berlin, Germany – Booth 13

Keynote speaker Martin Lush will open this event with the presentation – The Political Landscape and the Future of the Pharmaceutical Industry

### RAPS (Regulatory Affairs Professionals Society) Convergence

September 9-12, 2017

National Harbor, MD, USA

### PDA/FDA Joint Regulatory Conference

September 11-13, 2017

Washington, DC, USA

### Pharma Integrates 2017

November 15-16, 2017

London, UK

Martin Lush will be chairing two panel sessions

### Training – Making it Stick

September 18, 2017

### Leadership 2030 – What will it Take?

October 16, 2017

### Performing Under Pressure

November 13, 2017

FREE WEBINARS

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

A full, up-to-date course listing including our webinars is available online. Book your place at [www.nsf.org/info/pharma-training](http://www.nsf.org/info/pharma-training)



# Changing Behaviors to Reduce Risk and Costs

## The Problem

An NSF client reported high levels of microbial contamination on the gloved hands of fully trained operators working in the Grade A (Class 100) and Grade B areas. Batches had been rejected. The client's investigation identified inconsistencies in hand sanitization. However, retraining efforts failed and problems continued at a cost of over £1.2 million p.a. in lost time and unsaleable batches.

## The Solution

We took the client through our five-step behavioral change process and our 'B=M.A.T.H.' model (which states that to change **B**ehavior, you must provide the **M**otivation and **A**bility, plus a **T**rigger event, to make it a **H**abit).

**Step one:** Identify the specific behavior you want to change (in this case, improve hand sanitization)

**Step two:** Identify the causes of the existing behavior (poor or inconsistent hand sanitization)

Using NSF's unique set of tools and techniques we identified over 45 causes of inconsistent hand sanitization. SOP complexity, inadequate training, distraction, cognitive overload, poor sanitizer bottle design, inconsistencies in bottle location, a compliance mindset, and lack of risk awareness were all contributing factors.

**Step three:** Motivate people to change – provide the “what’s in it for me?” (WIIFM)

We took staff to the micro lab. They looked at (and smelled!) real bacteria. We linked the consequence of contamination to patient risk. We used a fluorescent dye test to help design a simple and effective way of removing bacteria from their gloved hands. After just two hours they left the lab motivated and their WIIFM question answered.

**Step four:** Make them able to change

People only change if the new behavior is easier than the old behavior. We took the client through our “brutal simplification” process and reduced their SOP from eight pages to just six bullet points.

**Step five:** Create the new ‘habit’

An old habit (behavior) can't be broken, only replaced by a stronger one. We built into the new hand sanitization SOP the components of the habit loop (the trigger-routine-reward). We then guided them through precise practice sessions until they sanitized their hands correctly and automatically.

## The Rewards and Benefits

After 12 months no further batches have been rejected. The client has also used the same five-step process to change other GMP and workplace behaviors. The client told us this two-day workshop was the best investment they have ever made.

### Your Call to Action: Want to Change Your Quality Culture?

- > If you want to achieve the same results, join our unique Changing GMP Behaviors course in June – visit **[www.nsf.org/info/pharma-training](http://www.nsf.org/info/pharma-training)**. If you want us to customize a behavioral change program to meet your specific needs, we can come to you
- > Visit our resource library **[www.nsf.org/info/pblibrary](http://www.nsf.org/info/pblibrary)** and read our Changing Your Quality Culture and Improving GMP Behaviors white paper from Journal 37 – **[www.nsf.org/newsroom\\_pdf/pb\\_changing\\_quality\\_culture\\_improving\\_gmp\\_behaviors.pdf](http://www.nsf.org/newsroom_pdf/pb_changing_quality_culture_improving_gmp_behaviors.pdf)**. You will also find other useful resources
- > For any more information contact Martin Lush (**[martinlush@nsf.org](mailto:martinlush@nsf.org)**)



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