Journal

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GETTING BACK TO BASICS

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welcome

Let's start this edition with a quiz. Just eight questions:

1. What must you do to prosper in an uncertain world?
2. What is the single biggest cause of data integrity issues?
3. Are data integrity issues the same in Europe as the U.S.?
4. How can a well-designed CAPA hierarchy reduce repeat deviations?
5. What do you know about our comprehensive eLearning on MDSAP country-specific requirements?
6. How many sections are there in the EU ATMP Guidance document and what do they contain?
7. What are the most recent regulatory changes and what do they mean to you?
8. How is our Advanced Program in Pharmaceutical Quality Management doing in India?

As always, I hope this edition of the Journal provides answers to many of the problems and challenges you face. My article ***The Future of the Pharmaceutical Industry*** (page 3) provides you with an opportunity to have your say. Don't miss out! When it comes to the ***perennial issue of data integrity***, George Toscano and Lynne Byers have all of the data and the answers. Just take a look at pages 6-8. Struggling with repeat deviations? Read Andy Barnett's unique guidance on ***Hierarchy for CAPA Effectiveness*** on page 9.

If you want answers to these questions and more, just keep on reading. We want this edition to be thought-provoking and it's packed full of useful tools and techniques to make your life easier. Please let me know what you think (**martinlush@nsf.org**). Your feedback is vital. If you want us to cover a subject close to your heart, please just let us know.

Remember: The Journal is YOUR Journal! Help us to make it even better.

Martin Lush

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

THE FUTURE OF THE PHARMACEUTICAL INDUSTRY

YOUR CHANCE TO CONTRIBUTE

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

Ever participated in one of those benchmarking exercises? You know what I mean. When a (usually) fresh-faced consultant asks lots of questions and fills in a spreadsheet comparing what you do with your competitors. Well, beware.

BENCHMARKING CAN BE DANGEROUS

Trying to copy and follow others in a world of turbulence and massive uncertainty is a risky business. Assuming that what worked last year will work in the future is also very risky.

I recently presented the 30-minute webinar The Political Landscape and the Future of the Pharma Industry available in our resource library (**www.nsf.org/info/pblibrary**) under Webinars. Some of what I covered is highlighted throughout this article. Of course, my predictions for the future are based on educated guesswork and whether they happen or not remains to be seen. After all, 20 years ago we were told to expect a paperless society, flying cars and more leisure time by now! The objective of my webinar was to get people thinking beyond the here and now.

The Future

The future looks great providing:

- We're honest about the challenges (the facts).
- We get back to basics and break old, outdated habits.
- We all help each other and collaborate like never before.

The Facts

- We have 7.5 billion people in the world who need looking after. Sixty-five percent of all healthcare spending in developed nations will be on those aged 65+. The over 60s will also be the most powerful political lobbyist in the world if they so choose. They are more likely to vote for politicians who promise to meet their healthcare needs.
- By 2025, 85 percent of the global population will be in emerging nations.
- Governments simply can't afford to treat the sick any longer. Prevention will be preferred over treatment. Pricing and reimbursement schemes will drastically change. Increasing levels of antibiotic resistance will render "routine" medicine redundant. Governments will have to take a radically different approach to pricing and reimbursement unless they want society to return to the pre-antibiotic era.
- Globalization, global warming, science and technology are all (for the first time in our history) accelerating at the same time. Everyone will be impacted. Drug shortages will continue, if not worsen, as supply chains are disrupted unless more is invested to improve resiliency.
- Medical technology will change our lives – 3D imaging, ultra-resolution microscopy, electronic patient records, computer aided diagnosis, low-cost gene readers and more. Wearable devices will put patients center stage and in greater control of their own healthcare.

- Short-termism will destroy corporations. Companies who run from one quarterly financial report to the next, ignoring the future, will not survive.
- Pharma currently spends, on average, $1.3 billion bringing a new medicine to market with an attrition rate of 90 percent. Clinical trial failures over the last five years cost the industry $240 billion. This level of inefficiency is not sustainable.
- Taking 15-20 years "from bench to bed" will not meet future healthcare needs.
- Much of the current regulatory framework is no longer fit for purpose and is guilty of stifling innovation when we need it most.

THE PACE OF CHANGE IN HEALTHCARE TECHNOLOGY IS FASTER THAN OUR ABILITY TO UNDERSTAND ITS IMPACT AND FASTER THAN THE REGULATORY STANDARDS AND FRAMEWORK.

- Eighty percent of university students are pursuing degrees for jobs that will no longer exist. Any job with any level of repetition (manual or cognitive) is at risk of being automated. Expect pharmacy, law and financial professions to look very different.
- Our world needs more economies of scale to achieve greater efficiencies. Expect to see more mergers (consolidation) and also demergers as mistakes are made.
- In Europe and North America, companies often struggle to find the talent they need. This is not the case elsewhere. More than 85 percent of the world's graduates in science, technology, engineering and math over the next two decades will be from Chinese and Indian universities.

- Although the impact of artificial intelligence (AI) in pharma is open for debate it will have a profound impact on healthcare. Did you know that one in 10 medical diagnoses is wrong? In some clinics AI can do a lot better. For example, AI is capable of predicting (with 80 percent accuracy) which patients would die of pulmonary hypertension within a year. Medics have only 20 percent accuracy. AI and wearable devices will allow medical interventions to be made earlier to cut back on treatment and hospital costs.

Back to Basics: How to Prosper in an Uncertain World

Excellence in any walk of life comes down to doing the basics to Ph.D. level. The companies that will succeed in the future will, in my opinion, do the following exceptionally well.

Leadership: Dynamic, Risk-Smart and Future Orientated

There is a big difference between leadership and management. Leadership is about doing the right thing. Management is doing things right. Pharma has relied too long on management. We need to recruit and develop risk-smart leaders at every level and get them onto the shop floor. Every leader needs to become a "futurist", not focused on the quarterly financials. The benefits and risks of AI are not being correctly assessed by many senior leaders because many know so little about developments in technology and science.

We Must Become Risk-Smart

Companies still talk about zero risk as if it's real. It's not. Zero risk is an illusion. In fact, risk aversion is dangerous. It stifles innovation, increases complexity and (paradoxically) risk. We must become risk-smart. We have to admit risks and manage them intelligently and quickly.

Simplification Is Survival

Remember less is more. When we have simple systems, motivation improves, errors fall and productivity increases. Simple systems also allow us to "fail fast". In times of uncertainty we will make lots of mistakes. These only become learning opportunities if we fail fast.

Stop Training and Start Educating

Most companies' training programs just tick the compliance box and change little. Old behaviors remain. If you understand 10/20/70 and NSF's model for behavior change, B=M.A.t.H, your future looks bright. Your education programs must focus on providing the skills that will matter most: emotional intelligence, risk-based decision making, critical thinking and problem solving. Certainly not GMP compliance.

From CAPA to PACA

When problems and errors occur, so many companies focus on the immediate correction. The "Band-Aid companies" who allow high levels of repeat errors and mistakes won't be around for much longer. The focus must be on prevention, not reaction, by designing out errors and mistakes in the first place and by brutally simplifying everything.

Change Management: Fast and Efficient

Unless your change management system can review and approve changes in less than an hour, you are going to be in trouble. In this turbulent world agility is key. Your change management system must be quick (otherwise it won't be used) and only approve changes that add value and reject the rest (usually 80 percent!).

Collaborate Like Never Before

I leave the most important and hardest to last. We will not meet future healthcare needs unless we all collaborate - regulators, industry, payers and patient groups. The latter have been ignored for too long. Unless we collaborate, we won't make it.

I still come across people and companies who are institutionally blind. They seem totally unaware and ill prepared for what is coming. Is it arrogance or ignorance? Who knows? For me it all boils down to simple economics:

> In 1960 healthcare represented less than 6 percent of the U.S. economy. By 2013 it had tripled to 18 percent of GDP. In the UK the total proportion of GDP dedicated to healthcare has increased from 6.6 percent in 1997 to 9.6 percent in 2010.
>
> If we as an industry fail to rise to the healthcare challenge, the results are likely to be soaring, unsustainable and a burden on us all.

Remember Your Task

- Listen to the webinar at your next team meeting. It's only 30 minutes long.
- Share this article with as many people as possible.
- If you have anything to add to The Facts and Back to Basics, please send them to me (martinlush@nsf.org). I will anonymize, collate and share in the next edition of the Journal.

We're all in this together. This is your opportunity to contribute. There are 7.5 billion people depending on us.

This article was first published on Pharmaceutical Online.

Further Reading Resources

- White Paper: Is Fear of Risk Your Biggest Risk?
- White Paper: What's the Difference Between 10/20/70 and 70/20/10?
- White Paper: Changing Your Quality Culture and Improving GMP Behaviors: What Works and What Doesn't – including information on NSF's B=M.A.t.H behavioral change model
- Webinar: The Art and Science of Simplification – How to Win Your War on Complexity

Visit **www.nsf.org/info/pblibrary**

Data Integrity | A Closer Look

by George Toscano, Vice President, Pharma Biotech Quality Systems, NSF International

Data integrity remains a perennial hot topic impacting the pharma biotech industry and the trend has been picking up steam; the number of data integrity-related warning letters has increased consistently since 2010. A number of new guidance documents came out in 2016 by FDA, MHRA, EMA PIC/S and the WHO and yet companies continue to grapple with data integrity issues.

FDA enforcement has been ramping up as evidenced by the number of warning letters citing data integrity deficiencies between 2005 and 2017 (see **Figure 1**). A clear uptick starts after 2010, which is no coincidence. FDA began incorporating data integrity into its Pre-Approval Inspection (PAI) process as one of the primary inspection objectives in 2010 as defined in its Compliance Program Guidance Manual 7346.832. Better training for inspectors, incorporating data integrity as an inspection objective and companies not having robust systems to ensure data integrity have contributed to this trend.

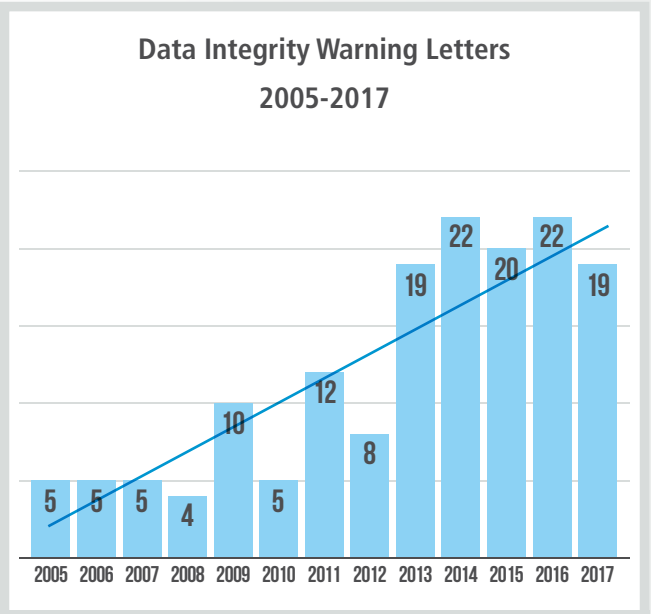

Figure 1

WHAT ARE THE MAIN ISSUES YOU SEE RELATED TO DATA INTEGRITY?

At NSF we have conducted extensive research into data integrity looking at our own clients, new guidance documents and regulatory enforcement actions. We decided to take a closer look to see where companies were struggling most. We reviewed warning letters issued from 2005 to 2017 for data integrity deficiencies. We then grouped these deficiencies into common themes and what we found was revealing (see **Figure 2**).

FINDINGS HIGHLIGHTS

Topping the list is **incomplete or missing records** which was cited 107 times in the 154 warning letters (67 percent). Examples include data being processed multiple times, but only one set being presented. Other examples include injections in a sequence which are not included in the data package; missing flasks, solutions or microbial test plates for tests that are supposed to be in process; or missing data to support analytical results.

Access control deficiencies were cited 50 times (32 percent). These include shared login accounts, users having inappropriate privilege levels such as administrator rights, and systems having inadequate controls that allow users to modify or delete files.

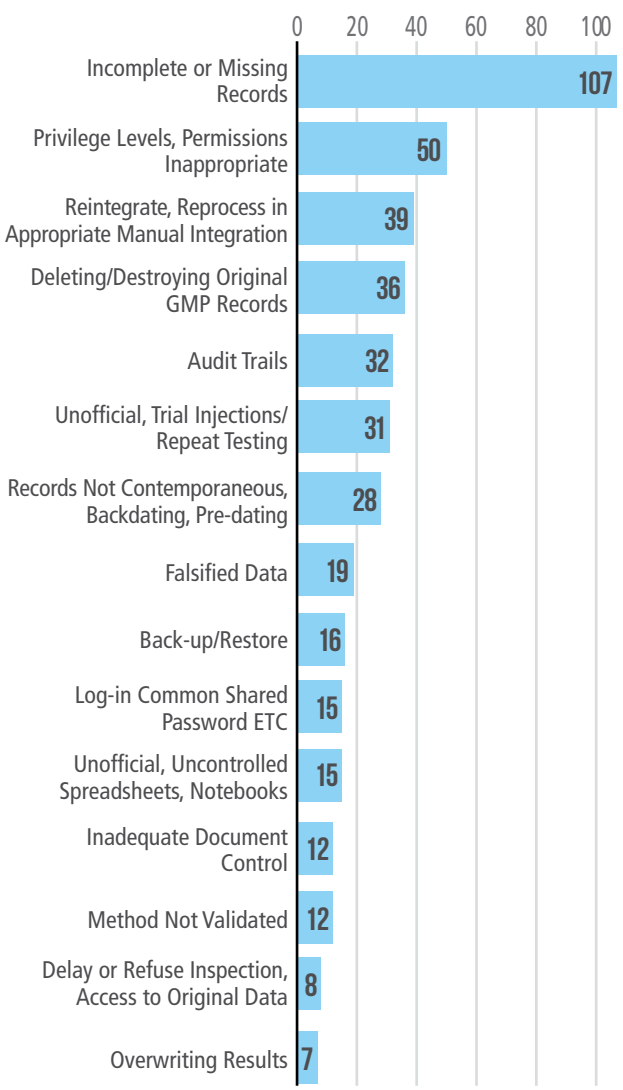

Figure 2

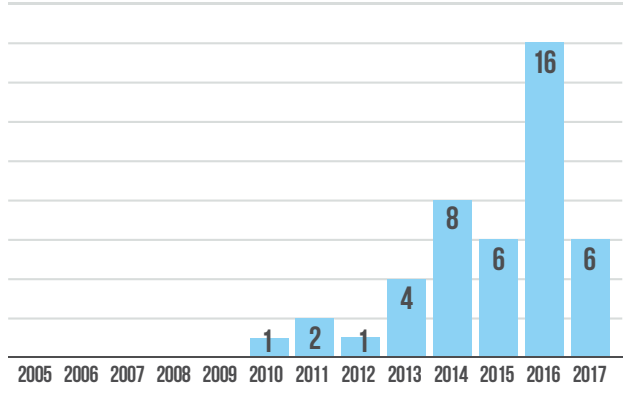

Figure 3

Reintegration, reprocessing and inappropriate manual integration was cited 39 times (25 percent). These include instances when samples are reprocessed multiple times with no justification and only one set of data is reported. This category also includes excessive manual integration with no justification or procedure to define the practice.

Deleting or destroying original GMP records was cited 36 times (23 percent). Items cited include analysts deleting data on electronic data systems as well as official records including sample notebooks and test records found in the trash.

Rounding out the top five, **audit trail deficiencies** had 32 citations (21 percent). Audit trail issues run the gamut from systems without audit trail capabilities, to audit trails being disabled by users, to audit trails not being reviewed to detect deletion or manipulation of data.

FDA RECOMMENDS THIRD-PARTY CONSULTING SUPPORT

FDA has been increasingly recommending that companies reach out to a qualified third-party consultant to help with addressing certain data integrity issues (**Figure 3**). NSF has served as an independent third-party on many occasions and is a recognized expert in this capacity.

WHAT ARE SOME OF THE CONSEQUENCES OF DATA INTEGRITY-RELATED FINDINGS?

Data integrity findings are taken very seriously by the FDA as they erode trust between the FDA and the company, and can result in FDA 483s, warning letters, import alerts, injunctions and, in severe cases, FDA invoking application integrity policy.

WHAT CAN COMPANIES DO?

Companies should first evaluate data integrity holistically and consider the entire data lifecycle when they think about data integrity and data governance. Secondly, companies should take a risk-based approach to addressing data integrity concerns, factoring in data criticality and data risk. The level of effort to mitigate data integrity gaps should be commensurate with the risk present.

I have seen many companies move along the data integrity maturity curve from initial awareness to basic understanding and ultimately to implementation of robust data governance programs. Most clients are struggling with implementation of data integrity concepts, and I am often asked questions such as:

- Do I need to review audit trails?
- How often do I need to review them?
- And what in particular should I be looking at?

We have helped many clients answer these questions and implement simple yet compliant solutions. If you feel that your company can use some help with implementation of data integrity controls, contact us at **USpharma@nsf.org** or **pharmamail@nsf.org** to discuss how we can meet your needs.

DATA INTEGRITY – IS EUROPE DIFFERENT?

by Lynne Byers, Executive Director, Pharma Biotech, NSF International

The level of detail about European regulatory inspections is not as fully available to the public as it is in the U.S. where warning letters are published. However, an excellent source of information is the EudraGMDP database, **http://eudragmdp.ema.europa.eu/inspections.** Here you may glimpse the reasons for suspending a GMP authorization.

European Data, Jan 2017-Feb 2018

16 Non Conformance Reports

Typical findings

- Reporting testing not performed.
- Issues with log in to computerized systems.
- System security in computerized systems.
- Falsification of records; e.g. test, calibration, sampling and manufacturing records.
- Falsification of location of manufacture.

An assessment of the data available in Europe would indicate that European regulators are finding the same issues as the U.S. FDA. At NSF we offer in-house courses on data integrity, as well as public courses in specific topics. For up-to-date information on our public pharmaceutical courses, visit **www.nsf.org/info/pharma-training**.

Watch NSF's latest video **Data Integrity – A Closer Look** available in our resource library (**www.nsf.org/info/pblibrary**) under Videos.

A special thank you to Andy Barnett, Director of Pharma Biotech Quality Systems at NSF, for conducting the research that made this article possible.

Hierarchy for CAPA Effectiveness

by Andy Barnett, Director, Pharma Biotech Quality Systems, NSF International

Have you ever reviewed an investigation report and wondered whether the proposed corrective and preventive action (CAPA) would be effective?

Sometimes, we shrug our shoulders and say, "At least they put something in place". We all know that the FDA expects us to include an effectiveness check, but do we have enough guidance to make these checks meaningful? NSF suggests that you consider these three questions:

1. What will you measure?
2. When will you measure it?
3. What is your acceptance standard?

Here are two examples:

- Three months after implementation of the CAPA, check for repeat incidents. If there are no incidents, close the CAPA. If there are repeat incidents, re-open the investigation.
- Ten batches after implementation, calculate the new average reject rate. The CAPA is successful if the reject rate is less than 1.5 percent. If the new reject rate is higher than 1.5 percent, re-open the investigation.

But are these requirements sufficient? Is there any way we can evaluate the CAPA *before* implementation? We will lose valuable time if we must wait three to six months for the answer. The regulatory risk increases as the clock keeps ticking.

We propose introducing a CAPA hierarchy that investigators can use to help them select an appropriate corrective/preventive action that is most likely to deliver the desired outcome. It can also be used by approvers. It may even give them additional leverage to push back for a better solution, or perhaps simply help them articulate the weaknesses they saw in previous CAPAs. After all, some corrective actions ARE more effective than others.

CAPA HIERARCHY

In order of *decreasing* effectiveness

1. Elimination
2. Replacement
3. Facilitation
4. Detection
5. Mitigation

Elimination

Eliminate the ***possibility*** of error. This can be accomplished by eliminating the task. For example, eliminate mixing errors by purchasing pre-mixed materials. Eliminate recording errors by linking the measurement device to a printer.

Elimination can also be accomplished by a poka-yoke (an error-proof device). This concept is wide-spread in manufacturing where a special fixture makes a part impossible to install incorrectly.

For example, I participated in an investigation for IV bags that were shipped to the customer without a thermal print label. Every time the operator pushed the emergency stop button, the printer and camera would lose their memory, so the printer did not know what to print and the camera did not know what to reject. We eliminated the problem by revising the PLC program to automatically reject the in-process bags following an e-stop. We also added a verification clause to the validation procedure.

Use your imagination to think of other ways to adopt poka-yoke to pharmaceutical production.

Replacement

Change the current process by **replacing** it with one that is more reliable. Examples:

- Design a more robust screen for milling machines so they don't break so often.
- Add redundant sensors on machines so if one sensor fails, the other will still work and the process is still OK.
- Replace human inspection with 100-percent automated inspection at the source. Install bar-code scanners.
- Install mechanical limiting devices or PLC programs so that a process cannot exceed a specified range.

Facilitation

Make the process easier to perform so that mistakes are less likely to occur. Examples:

- Use "visual factory" techniques such as 5S and color coding. Make errors more obvious.
- Redesign forms so they are easier to complete, and omissions are easy to spot.
- Use dedicated storage areas to reduce the possibility of material mix-ups.
- Reduce material handling. Every movement is an opportunity to make a mistake.
- Add pictures to procedures.

Detection

Improve detection by adding new or better sensors, at the source if possible. Examples:

- Add audible alarms or lights if a process is out of tolerance. Better yet, automatically shut down or add an interlock so the process cannot move to the next step.
- Use trending routines to signal before the process goes out of tolerance.

Understand that a corrective action that improves detection is inherently weaker than a corrective action that eliminates the problem. Why? Because detection does not prevent defects, it just prevents *escapes*. And defects cost you money!

Mitigation

Minimize the effect of the error. This is typically the weakest form of corrective action. For most companies, product designs are constrained. Probably the only way to mitigate is to sort or rework, but this should be viewed as an interim step, not a permanent corrective action. This is true even if you design a perfect automated re-inspection system. Rework is a crutch.

Sometimes you can combine detection and mitigation. Examples:

> Install a metal detector with a link to the conveyor. When metal is detected, mitigate by stopping the conveyor before contaminating the bin.

> Use a camera to inspect fill volume and link it to a reject mechanism.

Conclusion

Now that you aware of the CAPA hierarchy, I challenge you to consider reviewing a sample of past CAPA actions. How many fall into the detection and mitigation categories, which are the least effective actions you can take? I suspect that the percentages will surprise you.

Note that the CAPA hierarchy does not include retraining. Sometimes it is very difficult to find the root cause. Just be careful not to fall into the "blame and train" trap when you can't think of any alternative actions. Training is necessary, but not sufficient. What happens in six months when there is employee turnover? People are human, and people make mistakes. If training is one of the CAPA actions, just be sure to supplement it with at least one additional CAPA that falls into the CAPA hierarchy categories listed in this article.

Roll out the CAPA hierarchy to your organization and you will have a better chance of implementing preventive actions that deliver significant improvements. With the CAPA hierarchy, you can anticipate an effective outcome, rather than waiting several months for the CAPA implementation, only to be disappointed by the results of the effectiveness check.

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

To watch NSF's latest video on the CAPA hierarchy by Jim Morris, visit our resource library – **www.nsf.org/info/pblibrary**

You can also attend one of NSF's European residential training courses covering this topic:

> **Changing GMP Behaviors,** June 28 – 29, 2018

> **Incident Management Workshop,** September 11, 2018

> **Quality Risk Management,** September 25 – 26, 2018

And remember we can bring any of our courses on-site globally, and customize to your company requirements!

by Heather Howell, Executive Vice President, Training and Education, Medical Devices, NSF International

NSF Launches Comprehensive eLearning on MDSAP Country-Specific Requirements

Are you ready for Medical Device Single Audit Program (MDSAP)? Struggling to find training on all five MDSAP-participating countries' regulatory requirements?

It's finally here! NSF's Medical Device Global Regulatory Requirements training! NSF worked with former regulators and globally recognized experts from each of the five MDSAP-participating countries to bring you this comprehensive online training.

If you've wondered how you'll possibly learn the regulations of countries around the globe, and how you'll ever meet the new competency requirements, our new training courses are just what you need! Choose to complete one or all five of the country modules from our one-stop shop.

Marketing a medical device in a global environment offers many challenges, as regulatory requirements vary widely from one country to another. Bringing a product to market in multiple countries requires understanding the differences and knowing how to comply with regulations and procedures. This training series provides comprehensive instruction on the individual country's regulatory structure and the requirements necessary to bring a product to market in that jurisdiction… and to keep it there!

What is MDSAP? This program allows recognized third-party auditing organizations (AOs) to conduct a single audit that will satisfy the relevant regulatory requirements of all participating regulatory authorities. These authorities include Australia's Therapeutic Goods Administration (TGA), Brazil's Agência Nacional de Vigilância Sanitária (ANVISA), Health Canada, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and the United States Food and Drug Administration (FDA).

MDSAP audits save time and money by replacing multiple lengthy audits, allowing less interruptions in manufacturing schedules. In addition, Canada has deemed MDSAP certification mandatory for marketing as of January 1, 2019. With the increase in utilization of MDSAP, and the time constraint of Canada's looming deadline, it's essential that manufacturers and auditors understand the regulatory requirements of participating countries to ensure readiness for the MDSAP certification audit.

What is the training format? This series features country-specific requirements for Australia, Brazil, Canada, Japan and the

United States. These online courses offer highly interactive instruction on each jurisdiction's **legal and regulatory** framework, **premarket pathways** and requirements, and **postmarket regulations**. They also highlight specific country requirements that must be considered in conjunction with **MDSAP audits**.

Each highly interactive and engaging course in the series takes approximately 90–120 minutes to complete. Each course includes knowledge checks and final assessments, resulting in a *Certificate of Successful Completion*, demonstrating objective evidence of competency. This objective evidence is now a critical component of your company's training files, as required under the new ISO 13485:2016.

Why NSF courses? NSF's eLearning program offers you the flexibility to learn at your own pace, on your own schedule. Our flexible online modules are fun, interactive and available 24 hours a day, seven days a week. No worries about scheduling conflicts or costly travel expenses; we offer all your learning needs with the click of your mouse.

To develop these eLearning modules, we tapped into the knowledge of medical device experts from all over the world, with extensive regulatory, industry and notified body experience. The courses were then designed by skilled and licensed educators, making our courses a one-of-a-kind experience.

NSF International's medical device team understands our customers' needs and we're committed to providing the highest quality services. The depth and breadth of our global experts, along with our long-standing relationships in the international standards arena, means that we keep abreast of global trends and pending revisions. So, rest assured that in the constantly changing regulatory landscape, we will provide consistent training tools to keep you informed and to satisfy competency requirements.

For more information on the eLearning program, visit **www.nsf.org/info/md-elearning**

Tech Talk

Review of EU ATMP GMP Guidance

by Robert Smith,
Consultant,
Pharma Biotech,
NSF International

On November 22, 2017, the EU Commission adopted the Guidelines on Good Manufacturing Practice specific to advanced therapy medicinal products (ATMPs), as Part IV of EudraLex Volume 4. These guidelines come into force on May 22, 2018. When these GMP guidelines for ATMPs were first drafted, most of the manufacturers of ATMPs were critical of the guidelines being a separate guidance document rather than being an annex to the existing guidelines in EudraLex Volume 4. There were also criticisms from smaller academic and hospital units that the new guidelines place too much burden on these units in their rigid application of industrial type GMPs, which they argued was not practicable to these highly innovative products. Concern was also expressed that as the initial draft stood, the innovative research that was going on with ATMPs would be hindered in the EU.

Now that we have the final guidance document, it is interesting to see how these various concerns have been reconciled by the EU Commission.

The new guidance is 90 pages long and consists of 17 sections plus a glossary of terms. There are several sections in the guide that will be familiar to anyone working in the pharmaceutical industry.

These sections include:

- Pharmaceutical Quality System
- Personnel
- Premises
- Equipment
- Documentation
- Production
- Qualification and Validation
- Qualified Person and Batch Release
- Quality Control
- Outsourced Activities
- Quality Defects and Product Recalls

It is clear that in these sections, the authors have taken concepts that already exist in many of the chapters and current annexes and tweaked them for ATMP use. Therefore, one can argue that the authors could have pointed the readers to the existing GMP. However, these sections contain some very specific advice that is pertinent to the manufacture of ATMPs.

In the section Pharmaceutical Quality System, the guidance gives much more emphasis on using a risk-based approach, which is understandable given the nature of ATMPs which have highly variable starting materials and can be complex to manufacture. There is also a recognition that the manufacturing technologies are rapidly advancing, which means flexibility is required. The guidance does make it clear that patient safety must be the goal, even though a risk-based approach is being used.

Another major element of this section is the guidance given for investigational ATMPs. Key areas the guide concentrates on are patient safety and product quality and the need for data from early phase clinical trials to be used in later clinical trials. As with non-ATMP investigational product, the guide does accept that the levels of GMP will increase as the knowledge of the ATMP increases.

In the section Personnel, the guidance does state that a QP can be responsible for quality control (QC) or production, but not both. The guidance allows individuals in small organizations to perform both the production and QC role, though individuals are not allowed to QC test batches that they have manufactured. This is a clear divergence from the norms that we see in EudraLex Volume 4, Part I, Chapter 2.

The section on documentation places a lot more emphasis on the bidirectional tracking of cells and tissues from the point of donation, through manufacturing, to the delivery of the finished product to the recipient, as well as the requirements to keep data for 30 years.

The Production section of the guide concentrates heavily on the aseptic processing requirements for ATMPs, as this is seen to be a key requirement to patient safety. There is an acknowledgement of the fact that these products may have a very short shelf life. For example, manufacturing an ATMP can take place in an operating theatre where the time between donation and administration is very short.

The section on qualification and validation is another area of divergence from established GMP practice. The guide recognizes that there may be a shortage of starting material so when validating processes, there is an allowance to use surrogate materials and concurrent validation can be performed, provided this can be justified.

Another area of divergence from the current GMP guidance is around the QP and batch release. Section 11.10 states that there is no exclusion for the same QP to work for two or more sites, provided the QPs can provide their services to each site in a continuous fashion. There is a waiver for marketed ATMPs that are imported into the EU to forgo the testing on import, if there is limited ATMP or the ATMP has a short shelf life. Another area of divergence is the allowance for decentralized manufacturing, where "fresh cells" means that part of the manufacturing process needs to take place close to the patient. Under such

circumstances, there is a requirement to have a central site in the EU that has oversight of the decentralized sites.

The ATMP document also provides some specific guidance for ATMPs that is not found in other EU GMP guidance. One such area is starting and raw materials. There is a requirement that if antibiotics are used, they must not be in the final product. Guidance is also given on using cells that come from outside of the EU, as well as the use of xenogeneic cells and tissues which could transmit pathogens to humans. There is also guidance on the processing of starting materials and it's clear that the guide sees that final product quality is closely linked to the quality of the starting materials.

The guidance documents also provide specific information on seed lots and cell banks. These must comply with GMP and be established under appropriate conditions. There is a need for appropriate documentation to ensure traceability. Seed lots and cell banks must undergo safety testing to ensure they are free from adventitious agents. The guide also provides information on how seed lots and cell banks must be stored, which includes continual monitoring and alarm systems. The guide also states that is it desirable to split cell stocks and store them in different locations.

Reconstitution of product after batch release is also covered. The guide defines reconstitution activities and clearly states that they do not need to take place in a GMP environment. The guide also requires reconstitution activities to be justified and specifies that they can only take place at the administration site. The guide also requires the reconstitution process to be fully described with solvents and other materials being provided if they are required.

Another important section of this guide covers environmental control measures for genetically modified organisms that are ATMPs. In keeping with other aspects of the guide, the use of risk management is a key part of the strategy for ensuring these ATMPs are appropriately controlled and not released into the environment. There is an expectation that emergency plans are in place to deal with any accidental release.

The final section of the guide covers the automated production of ATMPs, which is becoming a common way of manufacturing ATMPs. There are clear requirements for equipment to be qualified and for there to be suitable operating instructions, regular calibration and maintenance of equipment and appropriate training of personnel. The guide also expects these automated processes to have a defined start and end and an expectation that where possible, critical process parameters should be continually monitored.

This new publication is a very comprehensive guidance document to companies and individuals manufacturing ATMP products. There is heavy reliance on utilizing a risk-based approach to manufacturing, which is not surprising as rapid advances are being made in this area. For example, therapies are now being developed where only parts of a cell are being administered to patients. The guide provides a pragmatic solution for small research institutes where the operational reality is that lines between production and quality control can be blurred, while retaining one of the fundamental principles of EU GMP, the role of the QP in the certification and release process. The guide also provides some pragmatism with respect to the fact that not many QPs are currently working with ATMPs. The one question that remains is how far the ATMP GMP guide will diverge in the future from the other GMP guidance as there is currently a lot of overlap.

Have a question on the article? Contact Robert at **robertsmith@nsf.org**.

Regulatory Update

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

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

EU News

EU GMP Annex 13, Investigational Medicinal Products

In December 2017 a revised Good Manufacturing Practice (GMP) for Investigational Medicinal Products (IMPs) was published as a revision to Annex 13 in response to industry feedback. As with the new GMP legislation, the revised Annex 13 will become effective on the date that the Clinical Trials (CT) Regulation EU No. 536/2014 eventually becomes effective.

In practical terms, the revised Annex 13 is not very different from the existing one, although the labeling requirements in the existing annex have been removed. Legislation references have been updated to reflect the new CT and IMP GMP legislation. The content has been re-ordered to fit with the order of the chapters in Part I of EU GMP (EudraLex - Volume 4) and removes some duplication that was in the current version by cross-referencing to either a chapter in Part I or in other annexes.

Implementation of Commission Delegated Regulation 2016/161, Safety Features

There is now less than a year until the implementation deadline of February 9, 2019 and there is concern as to whether all manufacturers and the national verification systems will be operational in time.

In February 2018 the European Commission updated its guidance on safety features to version 9. The new version clarified that if product is exported outside of the EU/EEA, the unique identifiers have to be decommissioned in the European Medicines Verification System (EMVS). If the product is subsequently re-imported into the EU/EEA, full import expectations (i.e. re-testing unless from a country with a mutual recognition agreement and QP certification) apply and the unique identifiers cannot be re-commissioned. This means that the product would have to be repacked and new unique identifiers, containing a new batch number and expiry date, will need to be affixed before it is released for sale and distribution within the EU.

In March 2018 the European Medicines Verification Organisation confirmed that only marketing authorisation holders, and not contract manufacturing organizations, will be given access to report to the EMVS. This restriction has the potential for delaying the upload of the unique identifier and other information to the EMVS.

EU-USA MRA

On March 1, 2018 the U.S. FDA announced that it had determined that it could recognize

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a further four European drug regulatory authorities as capable of conducting inspections of manufacturing facilities that meet FDA requirements: the Czech Republic, Greece, Hungary and Romania. Two more authorities are due to be added on June 1, 2018.

ICH News

New Topic, E17

In November 2017 the Management Committee of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) approved the establishment of a new group, E17, to work on a guide on the planning and design of multi-regional clinical trials (MRCTs).

Facilitating the conduct and acceptability of MRCTs is expected to have a direct public health benefit, by encouraging more predictability around the approval of trials and the use of clinical trial data from a greater variety of countries and regions. It is hoped that this will decrease the delay in marketing authorisation often caused by requirements to conduct trials in local populations, and promote earlier access to innovative medicines. Avoidance of duplicative regional or national trials will also avoid unnecessary trial subjects' exposure.

Brexit News

UK Position

On March 2, 2018 the UK Prime Minister, Theresa May, gave a major speech on Brexit in which she said that the UK would like to retain "associate membership" of the European Medicines Agency (EMA), which would allow the UK Medicines and Healthcare products Regulatory Agency (MHRA) to continue to participate in activities of the EMA. Within a week the European Council responded that this would not be possible, so it looks as though the MHRA will have to become a standalone UK agency post-Brexit.

EMA Move to Amsterdam

On March 5, 2018 the EMA published a tracking tool to allow stakeholders to follow progress with the move to Amsterdam. This tracking tool first gives a general overview of the main milestones agreed for each of the work streams, except for external communication, which is an ad-hoc activity dependent on the progress made with the other work streams. It then outlines in more detail the deliverables for each work stream, highlighting clearly if EMA is on track to meet them. These timelines are interactive, and users may find more information by hovering their mouse over each pinned deliverable. The tracking tool is a living document, in which milestones may be added as the project progresses. It will be updated every month. It can be found online on the **EMA website**.

Reallocation of Rapporteurs

The EMA announced on April 11 that, together with the remaining 27 Member States of the EU, it had completed the reallocation of the medicines for which the UK MHRA and VMD are currently rapporteurs or co-rapporteurs appointed by the scientific committees to coordinate the evaluation of a medicine.

Over 370 centrally authorized products have been transferred to new rapporteurs and co-rapporteurs from the 27 Member States, plus Iceland and Norway, following a methodology developed by EMA's working groups on committees' operational preparedness for human and veterinary medicines.

UK MHRA News

On March 9, 2018 the MHRA published the final version of their revised data integrity guidance. This updates their 2015 guidance, which focused primarily on GMP, to cover all GXPs (good clinical practice, good distribution practice, good laboratory practice, good manufacturing practice and good pharmacovigilance practice).

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

U.S. NEWS

ANDA/NDA Holders Now Must Inform FDA of Marketing Status

The FDA Reauthorization Act (FDARA), enacted on August 18, 2017, continued the five-year reauthorization cycle of the human medical product user fee programs (PDUFA, MDUFA, GDUFA and BsUFA). It also created a new FDCA Section 506I, Prompt Reports of Marketing Status, which requires the holder of an approved application to 1) notify the secretary in writing before withdrawing an approved brand-name or generic drug from sale, either 180 days before doing so or as soon as practicable, 2) notify the secretary within 180 days of approval if the drug will not be available for sale within 180 days of the date of approval and 3) review the information in the Orange Book and notify the secretary in writing that either all of the application holder's drugs in the active section of the Orange Book are available for sale, or that one or more of the application holder's listed drugs have been withdrawn from sale or have never been available for sale; and make sure each of these notifications include specified information (e.g. drug identity, reason for withdrawal from sale, etc.).

The one-time Orange Book review by all holders of approved new and abbreviated new drug applications (NDAs and ANDAs) was required 180 days after the FDARA approval or by February 14, 2018. A failure to submit this one-time report may result in the secretary moving the application holder's drugs from the active section of the Orange Book to the discontinued section, as authorized in section 506I. Also new, FDA must be informed if the drug is not being made available for sale within 180 days of approval.

The 180-day notification to FDA before withdrawing the NDA/ANDA drug from the market aligns with a similar 180-day notification period for many biologics (21 CFR 600.82) for a permanent marketing discontinuance or for a major interruption in manufacturing. These notifications aids agency awareness of potential future drug shortages, allowing it time to act to avoid the shortage.

FDA Enhances Its Oversight of Homeopathic Drugs

The practice of homeopathy is based on the belief that disease symptoms can be cured by small doses of substances that produce similar symptoms in healthy people. The market share of homeopathic drugs has increased significantly in the past years with a large majority of products sold over the counter including for use in children. FDA has indicated that it intends to now strengthen its regulatory oversight of certain homeopathic drugs, based on the recent draft guidance, Drug Products Labeled as Homeopathic, issued December 2017.

To date, FDA has not enforced its authority to review over-the-counter (OTC) non-prescription homeopathic drugs for safety and efficacy, which were excluded from the Drug Efficacy Study Implementation (DESI) and OTC review panels. Instead its oversight (see Compliance Policy Guide 400.400) has been limited to certain labeling requirements; compliance with standards for strength, quality and purity as described in the HPUS; and the requirement to be manufactured under drug cGMPs. FDA recognized that these requirements did not adequately address the products safety and efficacy: "A product's compliance with requirements of the HPUS, USP, or NF does not establish that it has been shown by appropriate means to be safe, effective, and not misbranded for its intended use".

The enhanced oversight by FDA does not mean that FDA intends to subject every OTC homeopathic drug to a review of its safety and efficacy data. However, FDA intends to take a closer, risk-based approach of those homeopathic products that pose a higher risk to the public. As outlined in the draft guidance, FDA will be reviewing products more closely, especially products that have reported safety concerns, are reported to contain non-Homoeopathic Pharmacopoeia Convention of the United States (HPUS) ingredients, are administered in ways other than oral and topical, promise to treat serious illnesses and life-threatening diseases rather than symptoms, and those aimed at vulnerable populations.

The increased oversight of this drug category is reflected in increased inspections of homeopathic drug product manufacturers and warning letters being issued.

FDA Invites Discussion of Novel Technology in Pharmaceutical/ Biotech Manufacturing

There has been some concern from pharmaceutical companies that want to adopt innovative manufacturing technology that its use will likely delay their Investigational New Drug (IND)/NDA/Biologics License Application (BLA). The concern is that FDA reviewers need additional time to review their applications to understand the impact of the new technology on product quality. As such, the industry has been hesitant to develop and implement novel technology that contains both technical and regulatory challenges. Today there is an FDA-initiated pathway for Center of Drug Evaluation and Research (CDER) products to meet with the agency ahead of IND/NDA/ BLA submissions for products produced using novel technologies. This allows FDA chemistry, manufacturing, and controls (CMC) reviewers and inspectors to familiarize themselves with the new technologies and determine how they may be evaluated within the existing regulatory framework.

CDER's Office of Pharmaceutical Quality (OPQ) created the formal Emerging Technology Program (ETP) in 2015 to promote the adoption of innovative approaches to pharmaceutical product design and manufacturing. There is a formal FDA guidance, Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization Guidance for Industry (September 2017), that provides the background, scope and process for this program. In addition, FDA has put in place a Manual of Policies and Procedures (MAPP 5015.12) to internally guide the OPQ and ETP team in conducting assessments of possible ETP technologies. Both are helpful to companies considering the program and can be quite helpful in discussing, identifying and resolving potential concerns about technology prior to filing a regulatory submission.

To be considered for the ETP, a sponsor would request a type C meeting with FDA, as outlined in the FDA guidance Formal Meetings between the FDA and Sponsors or Applicant, indicating "Type C meeting – request to participate in the ETP". The request would include a brief description of the proposed emerging technology; why it is considered substantially novel; how it could potentially improve the product's safety, identity, strength, quality or purity; a summary of the development plan; and a timeline for the regulatory submission. Some examples of technologies assessed by FDA's ETP team include continuous manufacturing of a drug substance or drug product, 3D printing manufacturing, continuous aseptic spray drying, advanced process control such as predictive modeling for process monitoring and closed-loop bioreactor control, isolator and robotic arm for aseptic filling, etc. In 2017 alone, the ETP team accepted 19 meeting requests, held 20 meetings and worked to approve the third application with continuous manufacturing, an NDA for a breakthrough therapy, in 5 months.

Forthcoming Courses & Workshops

What's Planned From Mid-June to September 2018

Pharmaceutical GMP
June 18 – 21, 2018
Manchester, UK
Course Fee: £2,370 excl. VAT

Quality Risk Management for Sterile Products
June 18 – 20, 2018
York, UK
Course Fee: £2,060 excl. VAT

Active Pharmaceutical Ingredients
June 25 – 29, 2018
Newcastle, UK
Course Fee: £2,880 excl. VAT

Changing GMP Behaviors
June 28 – 29, 2018
York, UK
Course Fee: £1,580 excl. VAT

Pharmaceutical GMP Audits and Self-Inspections
A CQI and IRCA Certified Training
GMP PQS Lead Auditor Course
July 2 – 6, 2018
Oxford, UK
Course Fee: £2,970 excl. VAT

The Role and Professional Duties of the Qualified Person
July 23 – 26, 2018
York, UK
Course Fee: £2,750 excl. VAT

Incident Management Workshop
September 11, 2018
Stansted, UK
Course Fee: £695 excl. VAT

Human Error Prevention Workshop
September 12 – 13, 2018
Stansted, UK
Course Fee: £1,390 excl. VAT

Statistical Process Control
September 11 – 12, 2018
York, UK
Course Fee: £1,580 excl. VAT

Statistical Testing
September 13, 2018
York, UK
Course Fee: £790 excl. VAT

Pharmaceutical GMP Audits and Self-Inspections
A CQI and IRCA Certified Training
GMP PQS Lead Auditor Course
September 17 – 21, 2018
York, UK
Course Fee: £2,970 excl. VAT

Quality Risk Management
September 25 – 26, 2018
Manchester, UK
Course Fee: £1,580 excl. VAT

EARLY BIRD OR MULTIPLE DELEGATE DISCOUNTS APPLY TO SOME OF OUR COURSES. PLEASE CONTACT US FOR FULL DETAILS ON ALL OUR AVAILABLE DISCOUNTS.

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

Course details are correct at the time of printing and are published in good faith. NSF reserves the right to make any changes which may become necessary.

NSF News...

Advanced Program in Pharmaceutical Quality Management – Series Two Starts in September 2018

Improving Profits and Compliance Is Possible

Due to the overwhelming success of the first series (a sell-out), we are holding another series of the Advanced Program in Pharmaceutical Quality Management (APPQM). In collaboration with the Indian Drug Manufacturers' Association, this unique, internationally recognized and independently assessed program is designed for Indian companies who want to succeed in U.S. and European markets. Series two starts in September 2018 and applications are now being taken.

Delegate Work Placement Programs

As part of the program every delegate completes a project that will benefit their company. Agreed by their company sponsors, delegates receive free coaching and consultancy support throughout the program. Successful completion of these projects will generate millions of dollars in savings by improving productivity and regulatory compliance.

Examples of project titles from delegates who attended series one include:

- Radical Simplification of Quality Systems to Reduce Human Error Events
- Improving Laboratory Productivity by Eliminating Non-Value-Added Laboratory Processes
- How to Develop and Implement a Learning Culture Using the 10/20/70 Approach to Ensure We Maximize the Skills and Resources of Our Entire Workforce
- Simplification of the Batch Manufacturing Records and Product Release Procedures to Improve Right First Time and Speed Up Batch Release

Register for series two now. Contact Melvin Rodrigues at **actadm@idmaindia.com** for further details.

Hear what a current delegate has to say:

"Networking with the people on this course has really showed me how every company has its own work culture and there is so much to learn from each other. The training itself was thought-provoking and gave me a reality check of sorts on how my company might not be focusing on the right areas and so we might be hitting a dead end as far as improvement is concerned."

Ankit Chordia, Medopharm

IN COLLABORATION WITH IDMA INDIAN DRUG MANUFACTURERS' ASSOCIATION

Dates for Series Two – All modules take place at Acharya College in Bangalore.

Module One: **Pharmaceutical Quality Management Systems – Best Industry Practices**
September 3 – 6, 2018 | Tutors: Mr. Martin Lush and Mr. Robert Hughes

Module Two: **Managing Change – Change Control and Deviations**
November 19 – 22, 2018 | Tutors: Mr. Martin Lush and Ms. Rachel Carmichael

Module Three: **Human Factors – Getting People to Follow the Rules**
January 21 – 24, 2019 | Tutors: Mr. Martin Lush and Mr. Peter Savin

Module Four: **Transforming Data into Information – The Practical Application of Statistics to Transform Your Business**
April 8 – 11, 2019 | Tutors: Dr. Pete Gough and Dr. David Young

Module Five: **Quality by Design, Process Validation and Technology Transfer**
June 24 – 27, 2019 | Tutors: Dr. Pete Gough and Mr. Bruce Davis

Planting Firm Foundations in India

After wrapping up another successful project, one of NSF's pharma biotech clients in India planted trees on our behalf.

UPCOMING EVENTS

- **PDA-FDA Joint Regulatory Conference**
  September 24 - 26, Washington, DC, US | *Table 39*
- **RAPS**
  October 1 - 4, Vancouver, Canada | *Booth 23*
- **CPhI Worldwide**
  October 9 - 11, Madrid, Spain | *Stand 3G63*

Did you know?

NSF International has provided services to Forbes' top 10 most reputable pharmaceutical companies in 2017 and to the top 20 of the Pharmaceutical Executive's largest companies by revenue in 2017.

Making Pharmaceuticals

NSF EXHIBITED AT BOTH MAKING PHARMACEUTICALS EUROPE AND MAKING PHARMACEUTICALS UK.

The NSF team was happy to meet many new and existing clients at Making Pharmaceuticals in Brussels, Belgium on March 13-14 and in Coventry, UK on April 24-25. The exhibitions featured companies that are fundamental to every stage of the lifecycle of a pharmaceutical product, and the conference covered the major topics and issues facing the pharmaceutical industry.

We had an open discussion at our stand on "how the mighty fall" which drew up many interesting conversations. John Johnson, NSF's Vice President of Pharma Biotech, has also put together an article on this topic which you can view in our resource library (**www.nsf.org/info/pblibrary**) under the Other category.

John also presented at both the European and UK event, and Lynne Byers, NSF's Executive Director of Pharma Biotech, presented a session at the UK event. John presented Modifying Human Behavior for Perpetual GMP Compliance, while Lynne presented Brexit – Are You Ready?

If you would like a copy of the presentations, please get in touch with **johnjohnson@nsf.org** or **lynnebyers@nsf.org**.

Qualified Person Delegate Dawn Douglas Receives George Gettinby Award

Dawn Douglas of Almac received The Professor George Gettinby Award for Outstanding Achievement in Mathematics and Statistics 2017 as part of NSF's QP training program.

The award commemorates the late George Gettinby who was one of the University of Strathclyde lecturers on the Mathematics and Statistics QP training module. NSF gives an award to the delegate who gets the highest mark in the module exam. Congratulations Dawn from the NSF team!

NSF Case Study

PREPARING FOR A REGULATORY INSPECTION

PROBLEM

A project had been running for ten years and had not had a regulatory inspection. There had been many staff changes and understanding the history of the evolution of the project was difficult.

SOLUTION

NSF ran a workshop with a cross-section of staff at the site. The workshop was very different from a mock-inspection approach. It was performed in an open collaborative manner to identify key topics that needed to be fully understood prior to any inspection.

We asked a key question to everyone who participated, "The project started about 10 years ago - why has it taken so long?"

The answers were rich and varied and would lead an inspector in many different directions. The most illuminating answers came from a few people who had lived through the project, mainly the staff working in the manufacturing area.

On completion of the workshop, the client:

> Understood that no one could comprehensively explain the evolution of the project.

> Had greater insight into who had most knowledge about the project history (and it was not the various project managers who had changed many times).

> Had a list of topics from which to prepare a storyboard to explain the history.

> Had a clearly developed action plan to prepare the site for its inspection.

> Had a clear idea about who was confident presenting to a regulatory inspector and who needed more coaching.

Key Message

Approach inspection preparation in an open and collaborative manner. Sites will have the answers to the questions if the right people are asked.

When to Call in External Experts

Companies typically call in external experts when:

> They have a new facility or product.

> The site is expecting an inspection from a new regulator.

> The site is having a re-inspection.

Europe:
The Georgian House, 22-24 West End, Kirkbymoorside, York, UK, YO62 6AF
T **+44 (0) 1751 432 999** F **+44 (0) 1751 432 450** E **pharmamail@nsf.org**

USA:
2001 Pennsylvania Ave, NW, Suite 950, Washington DC 20006, USA
T **+1 202 822 1850** F **+1 202 822 1859** E **USpharma@nsf.org**

www.nsf.org

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