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welcome

Firstly, I hope you and your loved ones are keeping safe and sane as we continue to navigate the COVID-19 pandemic.

A couple of weeks into the lockdown I went into our UK office in Kirkbymoorside (York) to check things over and water the plants. On the doormat was a letter of thanks and appreciation from the local town council, whose members had read an article about NSF in the press. The letter read:

"On behalf of the local community we would like to thank you for everything you are doing to protect us from COVID-19."

I must admit the letter stopped me in my tracks. It made me realize the importance of what we all do and the way our industry has stepped up to the challenge. Vaccine R&D has never moved at such speed. Our understanding of antivirals has never been better. Regulatory agencies have also played their part, working around the clock to approve new treatments at lightning speed. You've also managed to keep supplying your lifesaving medicines and medical devices, despite remote working and home schooling. Please, just take a moment to pat yourself on the back!

This edition of the Journal is about hope and optimism, and how we must rethink our ways of working. Sure, the challenges ahead remain significant, but look at what we've collectively achieved so far.

You can see all the good things NSF has been doing to help on pages 24-26, including how our colleagues in clinical research helped in fast-tracking antiviral therapies and vaccines through the regulatory process. Also check out a detailed regulatory update section on pages 18-23.

So, keep up the fantastic work you're all doing and please remember we're here to help no matter what.

Stay safe and sane!

Martin Lush

Martin Lush,
Global Vice President, Pharmaceuticals, Medical Devices and Dietary Supplements, NSF International

TIME TO THINK & ACT DIFFERENTLY

by Martin Lush,
Global Vice President,
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"Governments should plan for a global pandemic in the same way as they plan for war."

Bill Gates, 2015

One thing COVID-19 has given us is something previously in short supply – time to think and reflect.

As we navigate this uncertainty two things are certain.

No 1: We will get through this.

No 2: The Post COVID-19 Environment (PCE) will be very different.

Let's make sure it's better by making the right progress. COVID-19 is not a one-off, it's a painful warning, so let's not waste the opportunity to reflect, learn and improve. We can start by agreeing to ***rethink everything***.

1. We MUST listen more and learn faster

In 2003, SARS was the pandemic that didn't happen, infecting 8,600 people and killing 860. Its epicenters (Hong Kong, Toronto, Singapore) had robust public health systems able to implement mass quarantine protocols. Had SARS hit less-developed centers, it would have been catastrophic.

In West Africa the 2014-2015 Ebola outbreak killed and orphaned thousands and paralyzed economies. Since 2003 over 600 cases of H5N1 (bird flu) have been reported in 15 countries. More than 60% of H5N1 patients die.

Over the last 20 years, disease experts have identified dozens of new or resurgent pathogens. It's a biological certainty that pathogens will relentlessly assault our increasingly packed and connected populations. COVID-19 was not a surprise, it was predicted. To progress we must listen more and learn faster.

2. Time to rethink the things we take for granted

My Dad always said the most important things in life are those we take for granted; food in the shops, family and friends around the table and those responsible for making everything happen, from the delivery drivers and shop keepers to doctors and nurses. We must not forget the vital importance of healthcare systems capable of dealing with a crisis like COVID-19. As governments applaud our healthcare workers let's make sure this appreciation (and extra funding) lasts beyond COVID-19. Global healthcare in the PCE will need more funding, not less.

Additional resource:

> **Webinar:** Answers to Your Big Questions

3. Time to rethink what we're really capable of accomplishing

Elite athletes and soldiers are taught 'The 40% Rule.' When you think you can give no more, you're only operating at 40% of your capability with 60% still in the tank. Want proof? Look at what's been achieved in the last few months. Can we build a 4,000-bed hospital – the UK's largest – in nine days? No problem. Can we continue to manufacture our medicines and medical devices with 30% fewer staff? Certainly. We still have very tough times ahead so remember 'The 40% Rule.'

Additional resources:

> **Webinar:** Resiliency – How to Take the Hits and Bounce Back

> **White Paper:** Can You Take the Hits and Bounce Back Stronger?

4. Time to rethink supply chains and 'globalization'

COVID-19 has exposed the harsh reality that our supply chains were built for efficiency and profit, not resilience. Assuming the world to be predictable, companies embraced things like lean inventory management and just-in-time delivery while making no provision for risk. Will COVID-19 force companies to build-in redundancy? Will manufacturing move closer to home? Will industry question the wisdom of hyper-globalized, hand-to-mouth supply chains? Will artificial intelligence, predictive analytics and robotics have a bigger impact? After decades of getting longer and thinner, will supply chains contract and reconfigure for a bumpy new world? Reality check: resilience = surplus, and surplus = extra costs. Will companies and governments invest in robust supply chains in the middle of a global recession? Can we afford not to?

5. Time to rethink how we develop and manufacture medicines and vaccines

The world has asked "When will there be a vaccine?" They are astonished to hear "In 18 months at least." They're staggered by the cost ($1 billion), the timeline (12-15 years) and the failure rates (90%+). When I say processes have remained largely unchanged for decades, they can't believe it. We have 21st century science, managed by 20th century minds, regulated by 19th century laws. We must rethink how we develop drugs faster and cheaper without compromising safety.

Additional resource:

> **Rebels Vs. Clones:** Constructive Dissent in the Pharma Industry

6. Time to rethink global institutions like the WHO

Fighting an exponentially replicating virus requires a level of global cooperation that seems beyond our governments. Step forward the World Health Organization (WHO), a specialized United Nations agency with a broad mandate to act as a coordinating authority on international health issues like COVID-19. They've been warning us about the threat of pandemics for years. We didn't listen. Established in 1948, the WHO undoubtedly needs modernizing. Its reliance on voluntary and earmarked contributions is not enough when pandemics are considered 'high risk – high probability,' the WHO must be given the resources needed to deliver its mandate. COVID-19 is not a singular event, it's a warning. Our institutions need to be better prepared and react faster.

7. Time to rethink leadership fit for a chaotic, uncertain world. Peacetime vs wartime leaders?

In moments of uncertainty, people turn to trusted leaders for direction and reassurance. Events like COVID-19 expose two types of leaders: peacetime leaders and wartime leaders. The best, and they are rare, are those who can quickly alternate, depending on the circumstances. In times of peace and certainty they focus on growth, expansion and profitability across a broad range of activities. In peacetime, you can get away with tried and tested protocols, methods, processes and ways of working, including micromanagement and centralized decision-making. You also have the luxury of more time to gain consensus and reduce uncertainty before decisions are made. In wartime, it's about survival and resilience, by galvanizing the entire workforce around one mission. Wartime leaders are prepared to rip up the rule book and start again. They encourage a questioning attitude over blind compliance. They know decision-making must be faster than their competition, viral or otherwise. They delegate as much decision-making as possible to those on the frontline. They remove silos, flatten hierarchies, suspend non-critical activities and install quick feedback loops to fail fast and fail well. Throughout the crisis they balance honesty about the challenges with optimism and reassurance.

In peacetime, leaders often rise through the ranks through knowledge and competency. They've been prepared to lead in a predictable world. COVID-19 has removed predictable from the dictionary forever. In the PCE, acute supply chain shortages will need to

be managed and simplified. Some markets will be lost, others gained. An increase in falsified medicines and cybercrime will boost volatility. As we enter a global recession, politics will enter a new era of volatility. We need to select and prepare our leaders accordingly. We need leaders comfortable in managing uncertainty, ambiguity and risk with the resilience and agility to ignore the playbook and start again.

Additional resources:

> **NSF's 6-2-Fix-in-6 Video:** Decision-Making Under Pressure, Part 1

> **NSF's 6-2-Fix-in-6 Video:** Decision-Making Under Pressure, Part 2

8. Time to rethink complexity: Simplification is SURVIVAL

In an uncertain world, agility is more important than profitability. To be agile you must have simple systems and practices. Three years ago, I helped a client simplify their QMS. A 360-page batch record was slimmed down to 23 pages with over 200 signatures reduced to 23 that mattered. SOPs were reduced by 37%. The simplified deviation & CAPA system reduced repeat incidents by 52%. The streamlined change control system allowed changes to be approved within 30 minutes, not three weeks. Two weeks into COVID-19 they told me, "We've continued making product with 25% fewer people. We couldn't have done this unless we had focused on simplification. Simplification is survival." We must implement simple systems and ways of working that can adapt to the next surprise.

Additional resources:

> **NSF's 6-2-Fix-in-6 Video**: SOP Complexity

> **NSF's 6-2-Fix-in-6 Video:** SOP Simplification, Part 2

9. We MUST shift our thinking from predicting to reconfiguring

Most of our systems, practices and ways of working presume a level of predictability. COVID-19 is a red flag we can't ignore. We must accept that we face unpredictable threats and plan accordingly. We must reconfigure everything to roll with the punches, so we bounce back stronger. As described by Nassim Taleb, fragile systems are damaged by shocks and robust systems weather them. Our urge to reap efficiencies and impose our demands for unnatural predictability has damaged our resiliency. If we can't control the volatile tides of change, we must build better boats.

Your call to action

> Consider my top points of 'reflection' and how we must think differently

> Let me know what you think at **martinlush@nsf.org**

> Share with your network so we can help each other make the PCE a better place

There are decades when nothing happens and weeks when decades happen. This is a singular opportunity to rethink everything and make real progress. During the COVID-19 pandemic the UK developed a new habit. Every Thursday at 8 p.m. in cities and villages across the land, we stood on our doorsteps and balconies to applaud our healthcare workers. Streets, villages and towns have set up groups to stay connected. Will this continue in the PCE? I hope so. We must adapt to this new world and make it a better place.

Spoiler alert: Humankind has the habit of saying 'never again' and then forgetting.

Streamlining Pharma Operations in the Wake of COVID-19

by Jim Morris, Executive Director, Pharmaceuticals, NSF International

COVID-19 is shedding further light on pharmaceutical sourcing strategies and their inherent complexity. Consider the example of Gilead's ramp-up of remdesivir manufacture under FDA Emergency Use Authorization. Behind the scenes, Gilead is managing the production of an API in Canada, sourcing key starting materials from across the globe, and finishing the injectable product at a facility in La Verne, CA. The enormity of the task when the product is early in its lifecycle is substantial. And, consider the efforts of so many companies racing to bring vaccines and therapeutics for COVID-19 through clinical development, demonstrating safety and efficacy at speeds rarely seen in the past.

As these organizations source starting materials, active ingredients, excipients and other components, they will face pressure to reduce timelines and find ways to accelerate development, testing and launch. And they will do so against a background of regulatory agencies across the globe having to scale back their inspection oversight due to COVID-19. This does not mean regulatory and GMP compliance is not expected, on the contrary, it's incumbent on all companies to tighten internal oversight. This requires creativity and unleashing new ways of managing suppliers, scaling-up production, accelerating regulatory review cycles, and managing changes.

The following issues will undoubtedly take on added meaning and call for leadership's attention.

Product Supply Shortages

Finished product supply shortages in the pharmaceutical sector were already an issue and have been a significant source of concern for regulatory agencies. U.S. companies like CivicRx and the Phlow Corporation have stepped in to fill the void. And regulatory warning letters continue to require notice to the FDA of a potential supply disruption. COVID-19 has only exacerbated the situation.

This is the time to sharpen the focus on supplier risk assessment and supply chain strategy. Companies need to go beyond which components are single-sourced and those suppliers that have had a poor quality record, to concerns around the logistics of shipment and possible trade barriers that might prevent shipment from a country. This requires a careful review of supplier risk of the entire supply chain. As indicated above, regulatory bodies are sensitive to drug shortages and will work with manufacturers to facilitate the registration and approval of alternate sources.

Supplier Oversight

The on-site supplier audit may become a thing of the past. Forward-thinking companies will look to substitute the on-site audit with data which provides confidence in their suppliers' systems and performance. However, data about a supplier's performance cannot be downloaded or purchased. The data must relate to the supplier and the customer's relationship with that supplier. For instance, suppose your company is purchasing valsartan from a supplier in China. The data you require should be relevant to that API: batches manufactured, batches rejected, deviations, change

controls issued and importantly how they are testing for nitrosamine impurities upstream in the production process. The data must be granular enough to establish confidence in the source of supply and/or raise concerns which warrant further evaluation.

Moving towards a more proactive, data-centric approach to managing supply chain risk is a welcome change. There will always be a need for an on-site audit, however COVID-19 is demonstrating supplier oversight can be accomplished remotely if you ask the right questions and the relationship with the supplier is built around transparency.

Personnel Impact

The virus is an invisible foe, as is the unseen stress on people in the workplace. I have heard the term "COVID vacation" used to describe working from home. For managers on the frontline leading unit operations where people are undoubtedly concerned about their well-being and that of their families there is no rest. They are managing higher levels of absenteeism, onboarding new employees virtually, and triaging issues to keep production schedules on track.

Every crisis breeds opportunity. If there's a silver lining it will lie with those employees who stepped forward for their colleagues and found creative ways to get things done. Or it may lie in the cross-training of employees for new or expanded roles. Key decisions around product quality may be delegated closer to the unit operation which should result in efficiency gains. However, employee knowledge gaps will become more apparent when a key subject matter expert (SME) is not available.

Knowledge and skill shortfalls should be tracked as this will inform training curricula. If someone has stepped into a new role and/or interim role, additional check points or huddles will be warranted.

Triage Management

Risk-based decision-making during a time of crisis takes on new meaning. Quality systems (deviations, change controls, product complaints) are categorized on the basis of risk. The degree of effort required to investigate and document findings is commensurate with the degree of patient safety risk. Under COVID-19 two things will happen: A) resources will become more scarce and B) the number of issues and severity of those issues will increase. Thus, organizations need to rely on their most competent managers to triage and focus their effort on those issues which will make the most significant difference to the organization. And they must do so with excellent understanding of their products, processes and regulatory requirements.

Inspection Readiness

The first inspection post COVID-19 requires special preparation. It's important to keep in mind that your organization or unit is only as good as its last inspection. Therefore, it's incumbent on each organization to treat its upcoming regulatory inspection as its first inspection. The list of issues will undoubtedly be unique and include conditional release of components, shipments under quarantine, deviations in transit, and a number of challenges which had to be managed under the stress of fewer people, newer people and people working at a distance.

Good companies emerge stronger after a crisis and we can predict that their regulatory inspections post COVID-19 will go well. Other companies will struggle and have difficulty explaining the rationale for the decisions taken during a period of intense pressure. We recommend starting your inspection planning now as opposed to a few months or weeks before an anticipated inspection.

Takeaway Message

Companies are adjusting to new ways of working under COVID-19. In pharma operations, these adjustments range from identifying alternative suppliers, conducting supplier audits remotely, expediting prior approval manufacturing changes, and shifting teams and roles as needed to keep product moving. Furthermore, regulatory agencies are adjusting their activities, from application review to compliance oversight.

We recommend taking stock of these adjustments and determining which changes should be embedded into operations. Operational efficiency gains in the short term due to handling COVID-19 could represent long term efficiency gains for individual companies and for the industry.

Have a question on the article? Contact us at **healthsciences@nsf.org.**

Who was it who said, "Necessity Is the Mother of Invention"?

by John Johnson,
Vice President, Pharmaceuticals,
NSF International

Even though NSF International is known for providing practical solutions for difficult situations, it's fair to say the last six months have been a testing time for everyone. Experts suggest COVID-19 may never be totally eradicated, and other pandemics are now seen as a probability rather than some form of science fiction. As a business community leader, we've kept close watch on how businesses (large and small, pharma, medical devices and others) are adapting to the new normal. And as with anything complex, the more you look, the more problems reveal themselves. Every day we're getting more accustomed to asking ourselves:

> *"Are my daily decisions adding risk to myself, my family, my organization or to my immediate society?"*

> *"If I take this course of action, do I enhance or detract from the quality of life of people close to me and do I make my organization more or less successful in the long term?"*

So how is NSF adapting to COVID-19? The simple answer is we are listening to our clients and we are changing how we work to suit their needs, now and for the long term. We allow our industry colleagues and clients to drive our services, at the same time as keeping them informed of best practice, regulatory trends and changing cGMP and quality system expectations. Effective communication requires more reception and very well-chosen transmission; i.e. listen more and speak only when there is something valuable to say!

What we have done to adapt to changing client requirements:

> When travel and hotel restrictions came into force, we modified more than 80% of our instructor-led, face-to-face training events to virtual, blended learning. We reskilled in the software so that we could redesign courses from scratch, gaining best use of the technology to enhance interactivity, promote online discussion, problem-solving and knowledge transfer. We knew time was tight for many of our clients, so we refined and simplified the key learnings, improved the visuals and made the training more targeted.

- We knew our international delegates couldn't travel, so our virtual courses are now often presented at a time zone ideal for most delegates, so you can attend and play your part in improving world health. If that's at 4 a.m. for us, then you've got it.
- We knew many projects, clinical trial supplies, diagnostics production, scale-up and technology transfer depended on timely, detailed supplier audits; and travel and hosting restrictions could impact the timing of vital audits. We devised a four-step approach for remote and virtual auditing that allows milestone audits to be performed to the best possible levels of insight and risk mitigation.
- Following some rapid training for our team, we got comfortable with performing a range of consultancy support via video conference and remote review, so we could be available when you needed us.
- We changed our communication schedule to focus on what our clients really needed during a crisis. We generated white papers, videos, webinars and podcasts on resilience, communication methods under pressure, dealing with seismic changes in available resources and crisis management. We pivoted every message to align with the changing needs of our clients.

We learned a lot from this, including:

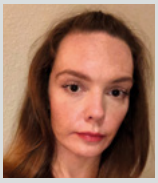
- 'F2F' video communications are much more engaging than a telephone call – and what's more, it can be fun. We're using technology for team building, shared activities, mentoring and just simply for looking out for each other. In these strange times, seeing a smiling, familiar face and 'shooting the breeze' can be a truly important part of someone's day.
- Characters are not made by a crisis, but they are revealed by one. We've learned just how amazingly capable and resilient our team is; and when tested we're sure you see this too. In a crisis, it's clear who's rowing the boat, who's dead weight and who keeps drilling holes in the hull. These insights reveal themselves and must not be overlooked.
- At times in this pandemic, we've noticed that clients are rightly consumed by the need to survive, to maintain an important supply chain or introduce a key medicinal product. Rather than distracting clients from these imperatives, we've diverted our resources to listening, supporting and working on business infrastructure. Someone here called this, 'painting the ceiling, whilst it's raining outside!' – essentially getting ready and making improvements for when the sun shines again, and clients are accessible, investing and planning for a more definable future. If you haven't started this yet, now's the time to get those jobs done and ready for the months ahead.

What has been key to us is our desire to keep listening, keep responding and keep innovating in tune with a quite different world ahead. Going through a paradigm shift doesn't change the basic want to serve clients and make a difference, even if the methods needed to achieve that need to be different. And crucially, all organizations and businesses (by design or good fortune) are clearly seeing who is making a positive impact on the business and who is not.

Watch out for the people on your team; can you see clearly who are the "energy providers" and who are the "energy sappers"? Maybe it's time to recognize both and act to surround yourself with the best team possible.

We'd love to hear the key things your organization has learned. Get in touch with us on LinkedIn or at healthsciences@nsf.org.

Safety Risk Management: A FRAMEWORK FOR DEVELOPING AND IMPLEMENTING REMS MODIFICATIONS AND REVISIONS



by Deborah Cole,
Marketing Associate, Amarex Clinical Research, LLC,
an NSF International company

& Shide Badri,
Safety and Pharmacovigilance Professional

Rapidly evolving safety risk management processes increasingly dictate drug approval and post-marketing surveillance[1]. To meet FDA requirements of developing and implementing changes to risk-evaluation and mitigation strategies (REMS), and to streamline this complicated process, we have detailed a framework of key concepts, standards and submissions procedures.

In 2007, the FDA Amendments Act (FDAAA), which amends the Federal Food, Drug and Cosmetics Act (FFDCA) to include post-market safety activities within the process for the review of human drug applications or supplements, introduced REMS to assure safe use of certain drugs. As defined by the FDA, "A REMS is a required risk management plan that uses tools beyond the prescribing information (the package inserts) to ensure that all benefits of certain drugs outweigh their risks" (U.S. Food and Drug Administration, 2019, p. 2). Without REMS some drugs could not be approved because of high safety risks. Prior to the REMS programs, a few products used risk minimization action plans (RiskMAPs) to the same end[2]. REMS supersedes RiskMAPs. The most extensive components of a REMS program are elements to assure safe use (ETASU), developed to mitigate specific and serious risks. Examples of common ETASU include:

> Prescribing physicians require more training or certification (e.g., to mitigate risk of severe allergic reaction)

> Patient monitoring for evidence of safe-use conditions (e.g., liver function monitoring to mitigate risk of liver damage, pregnancy screening with a negative result to mitigate risk of severe birth defects)

> Required enrollment in patient registry

Safety measures of a REMS are unique to a drug's associated safety risks. The FDA can require a REMS at any time, pre- or post- approval, and a REMS can be required for a single drug, or for a class of drugs. While the FDA is responsible for reviewing and approving REMS programs, sponsors are responsible for developing them. When deciding if a REMS is needed, consider the following factors[3]:

> Population size

> Seriousness of the disease

> Expected benefit

> Expected treatment duration

> Seriousness of known or potential adverse events

> Novelty of the drug

REMS REVISIONS, MINOR MODIFICATIONS AND MAJOR MODIFICATIONS

When new safety information becomes available, changes to a REMS may be proposed to ensure that a drug's risk-to-benefit ratio is acceptable. Changes to a REMS may also be proposed to reduce the burden on healthcare professionals of complying with the REMS. Changes to REMS are categorized

as REMS revisions, minor REMS modifications and major REMS modifications, depending on degree of potential effect on serious risk, safe use and the actions necessary to comply with the REMS[4]. Each REMS category has different submission criteria and regulatory action requirements (See Table 1 below).

Table 1. SUBMISSIONS CRITERIA, EXAMPLES AND REGULATORY ACTION FOR REMS CHANGES[4]

	Criteria	Examples	Regulatory Action
REVISIONS	> Changes are editorial in nature, and > Do not affect information in REMS materials regarding serious risk or safe use, and > Do not affect actions that must be taken in order to comply with the REMS	> Updates to contact information > Changes to International Classification of Diseases code > Changes to approved package count configuration requiring changes in the REMS materials	> REMS revisions must be submitted in the annual report
MINOR MODIFICATIONS	> Changes have a limited effect on information in REMS materials regarding serious risk or safe use, and > Changes have a limited effect on actions that must be taken in order to comply with the REMS	> Adding an approved new strength or dosage regimen > Adding an authorized generic > Graphics changes, including logo changes > Changing REMS call center hours of operation	> REMS minor modifications must be submitted as a changes being effected in 30 days (CBE-30) supplement
MAJOR MODIFICATIONS	> Changes have a substantial effect on information in REMS materials regarding serious risk or safe use, and > Changes have a substantial effect on actions that must be taken in order to comply with the REMS > Or safety labeling changes that modify a REMS	> Changing an element to assure safe use (ETASU) that modifies the verification process for dispensing the drug > Changing language in prescriber training materials to include safety labeling changes made to the package insert	> REMS major modifications must be submitted as a prior approval supplement (PAS)

ESSENTIALS TO SUBMITTING AND IMPLEMENTING PROPOSED REMS CHANGES[4]

1. If needed, seek advice from the FDA before submitting a proposed REMS modification.
2. Include a REMS history outlining all changes made to the REMS since original approval.
3. For minor and major modifications, except for FDA-required submissions, submit adequate rationale for the change. Detailed instructions for specific causes are provided in the FDA's Guidance for Industry, Risk Evaluation and Mitigation Strategies: Modifications and Revisions (U.S. Food and Drug Administration, 2019, p.13).
4. REMS revisions can be implemented immediately upon FDA receipt of the submission; no action is required from the FDA for this type of change.
5. Minor modifications can be implemented 30 days after FDA receipt of the submission; however, the FDA has 60 days from receipt of the submission to review and act on minor modifications; therefore, changes are not considered final until FDA approval.
6. Major modifications cannot be implemented until the FDA approves the proposed changes. The FDA has 180 days after receipt of the submission to review and act on proposed major modifications, with the exception of major modifications due to safety labeling changes that are considered conforming. In this instance, the FDA has 60 days after safety labeling changes are approved to review and act on the proposed major modifications. The 180-day time frame, following approval of the safety labeling changes, applies to major modifications due to safety label changes that are not considered conforming.
7. REMS for NDAs and BLAs require assessment of effectiveness of its safety measures at 18 months, three years and seven years after a REMS is approved, documented in a timetable to be included in the submission application. Assessments inform sponsors of the necessity of continuing a REMS program or modifying it.

CHALLENGES TO THE DEVELOPMENT AND IMPLEMENTATION OF REMS

> Developing and implementing a REMS program is time-consuming and costly, which affects sponsors, healthcare providers and patients.

> No two REMS programs are alike; each has different requirements and challenges.

> Added REMS requirements can unduly burden patients and providers.

> Recently published FDA draft guidances direct sponsors through the development of a REMS assessment plan and the execution of REMS assessment surveys, however these tasks remain difficult and intimidating.

PINSIGHTS BY NSF

Did you know that our safety risk management experts have been successfully submitting REMS programs and changes to the U.S. FDA since the program's start in 2007? Our safety and pharmacovigilance department can take your product through even the most complicated REMS program changes.

CHALLENGES TO REMS DEVELOPMENT AND IMPLEMENTATION DUE TO A PUBLIC HEALTH EMERGENCY (COVID-19)[5]

During and for the duration of a public health emergency (PHE), the FDA may impose temporary policies for certain REMS requirements. To ensure that timely response efforts meet patient needs in such situations, healthcare professionals, sponsors, regulators and other relevant parties should closely monitor FDA announcements and communicate with the FDA if needed.

In March 2020, specific to the COVID-19 pandemic, the FDA issued a new guidance addressing completion of REMS program ETASU requirements that may negate public health interventions for self-isolation and quarantine. This guidance states that laboratory testing or imaging studies required by some REMS can put patients and the public at risk of COVID-19 transmission and advises that "healthcare providers prescribing and/or dispensing these drugs should consider whether there are compelling reasons not to complete these tests or studies during the PHE, and use their best medical judgment in weighing the benefits and risks of continuing treatment in the absence of laboratory testing and imaging studies." (U.S. Food and Drug Administration, 2020, p. 7). The guidance indicates that these accommodations should be documented and summarized in the REMS Assessment Report.

As information becomes available on COVID-19 and safety risk management, other temporary policies for certain REMS requirements may arise.

We cannot over-emphasize the importance of safety risk management. Regulators have expanded submissions requirements to include REMS programs for certain high-risk products to maintain patient safety, and sponsors must keep up with the rapidly evolving changes. To navigate complex REMS requirements and challenges, let Amarex's safety and pharmacovigilance experts plot your REMS strategy course. We have extensive experience designing, executing and managing a broad range of REMS programs across many therapeutic areas. Dedicated to patient safety, our staff proactively track risk-management-related regulatory, legislative and market concerns, keeping us ahead of safety issues. Since 1998, Amarex has developed efficient, cost-effective product development solutions, tailored to our clients' needs.

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One Year of Regulatory Training Abroad:

KOREAN MFDS STAFFER WORKING AT U.S. CRO SHARES HER EXPERIENCE

Interviewer

Patrick JP Burke
Senior Director, Business Development

Interviewee

Na Ry Woo
Korean Ministry of Food and Drug Safety (MFDS) Scientific Reviewer

BACKGROUND

The Korean Ministry of Food and Drug Safety (MFDS), the Korean equivalent of the U.S. FDA, has a number of international cooperation programs designed to help key staff better understand global medical product development practices. Through one such program, Na Ry Woo, an MFDS Scientific Reviewer, is spending a year in the United States increasing her knowledge of medical product development practices of a U.S. Contract Research Organization (CRO) and of U.S. FDA regulations.

Na Ry's host organization is Amarex Clinical Research, LLC, an NSF International company, a CRO located in Germantown, Maryland. Amarex helps biotech, pharmaceutical, medical device, diagnostic and vaccine companies obtain U.S. FDA and international marketing approval of their new medical products.

Arriving in the U.S. in November 2019, Na Ry and her family started their American adventure in temporary quarters in Germantown.

Patrick: Na Ry can you describe the Korean MFDS and the training program in which you are participating?

Na Ry: The MFDS is a governmental regulatory agency responsible for market authorization of drug products, biological products and medical devices in Korea. I am working as a scientific reviewer of drugs within the cardiovascular and neurology product divisions at MFDS. The Korean and U.S. medical product regulatory systems are similar, and continued collaborations with the most developed foreign agencies, especially the U.S. FDA, helps the MFDS to maintain and grow its regulatory system.

Patrick: How did you come to be at Amarex?

Na Ry: I was very excited when I learned that I was accepted into this training program. It was difficult finding an appropriate training organization. From the outset I planned to get my training at a CRO as it's the most appropriate organization for learning U.S. FDA policies and procedures. I later

learned that Dr. Heemin Rhee, a former U.S. FDA pharmacologist, current consultant and U.S.-Korea liaison within the biotech and pharma industry, recommended me to my sponsor organization, Amarex. Dr. Rhee's relationship with Amarex developed several years ago because Amarex has done a lot of U.S.-Korea biotechnology collaborating for global drug development. Dr. Rhee made the suggestion and they immediately began preparing for this working relationship and started the visa process so that I could move to the United States.

Patrick: Where do you live now, how did you find your new home, and who came with you from Korea?

Na Ry: I came with my immediate family, which includes my husband and two daughters. We live in an apartment in Rockville, Maryland. A senior colleague, who had completed a two-year training program at the U.S. FDA, recommended the location. The experience so far has been very special to me and my family.

Patrick: How are you and the family adjusting?

Na Ry: My children are in the local elementary school and they enjoy the experience. It makes me very happy that they have such a unique opportunity. They are very fast at learning English too because their classmates are so kind and happy to help my girls. My husband is their primary caregiver while I work, and he enjoys spending time learning English also. We go sightseeing at every free moment, trying to soak up the American experience. My friends at Amarex say that I go out and enjoy the U.S. life much more than they do!

Patrick: Now that you have been working at Amarex for several months, what are the highlights of your experience, both at work and outside of work?

Na Ry: I work in the Regulatory Affairs department. My work consists primarily of preparing documents for submission to the FDA and this has given me a better understanding of the FDA submission process. I also participate in regular departmental meetings to learn about all ongoing regulatory activities that Amarex handles. It is a great place to work. Many of the employees are international and I enjoy the social activities that I participate in with my colleagues. We have many celebrations here, such as a monthly office 'social hour' and traditional U.S. holidays. Outside of work, I spend more time with my family now than I did when we were in Korea. In Korea our schedules are so different that we don't often have dinner together. We are getting to know each other so much more in this experience.

Patrick: What, if anything, has been difficult for you?

Na Ry: English is my greatest difficulty. It is a barrier for me, it is hard to understand what people are saying in conversations. I expect that after one year of training here, I will be fluent in English and I will be able to speak and understand the language freely.

Patrick: Have you met other Korean speakers here in Maryland?

Na Ry: Yes, in my second week I attended a meeting arranged by the Korean Trade Investment Promotion Agency (KOTRA) with the Maryland state Department of Commerce and I met several representatives from five visiting Korean biotech companies. The following day I attended a conference hosted by the Korean American Professional Association of Life Scientists (KAPAL), where I met many Korean scientists and a few other MFDS trainees. A friend and colleague, Dr. Haeyoung Ahn, has also kindly offered ongoing advice and encouragement during my stay in Maryland. Dr. Ahn is a former FDA Deputy Director of the Division of Pharmacology-3. She now works as a consultant to Korean biotech and pharmaceutical companies.

Patrick: I understand many Korean names have a particular and special meaning. Does your name have a particular meaning?

Na Ry: Yes, Korean names usually do have a particular and very special meaning, but my parents just wanted my name to be easy to pronounce so it does not have a special meaning. I notice that my American colleagues do not have difficulty pronouncing my name, so that is a success. There is a flower called Nary in Korean though, so you could say it is a type of flower.

Patrick: Thank you Na Ry. We look forward to another interview with you near the end of your training to learn about your complete experience.

Staff Spotlight

by Sam Richardson,
Senior Marketing Specialist,
Pharmaceuticals and Medical
Devices, NSF International

Sam caught up with Emma Ewins, NSF's new Director of Pharmaceutical Services, in a virtual interview.

Meet Emma Ewins

Tell us a bit about your background before joining NSF.

Lockdown photo!

I started in the pharma industry straight from school when I was 18 through a year in industry scheme, joining Lonza. I worked in the QA department and really enjoyed it. I ended up working at Lonza for three years which gave me good insight into the organization and a real passion for the industry.

I then decided to step out and go to university at 21 to do a biochemistry with biotechnology degree so was thankful for the scheme. I was viewed as a 'mature' student at only 21 which was odd!

What did you do after university?

After university I got a job at UCB in Slough in an outsourced manufacturing role. I looked after the supply chain from raw material through to the finished product. Over the next eight years, I held other manufacturing roles in both Lonza and UCB before moving to BTG Specialty Pharmaceuticals in 2009 where I worked in the chemistry, manufacturing and controls department covering outsourced manufacturing for multiple dosage forms.

As I progressed in BTG, I managed a process development team and moved to the BTG Wales site. I then progressed to director of manufacturing and into a site director role. Leading a manufacturing site was a really good experience. I was at BTG for almost 11 years in distinct roles, it was really good to be involved directly on the manufacturing side of things.

The same boss who asked me to move to Wales then asked, "Why don't you do your Qualified Person training with NSF?" I started the journey to become a QP in 2011 and I finished the training in 2018; it was a prolonged period as I had a son in between. So that was my introduction to NSF!

I was very grateful for all my opportunities at BTG, my last role with them was VP of quality and technical services for the spec-pharma business.

Do you have any career highlights?

My career highlight was the site director role. This was a big opportunity for me, going from a direct operational role in a technical commercial setting, from getting batches out the door to moving into a people-person role. In this role I had to do a lot of coaching, listening, constantly having my door open and I did a lot around engagement – it was a very different "me" and a real highlight.

One thing I'm quite passionate about is getting young people into STEM subjects. In this role I did a lot around STEM which is something I'd like to bring to NSF; I went out into the community and schools and did talks. I also started off an apprenticeship scheme and one of the things that drew me to NSF was the education element; the coaching and engagement side of things.

Are there any challenges you've had to overcome?

Being in an operational role you have many daily challenges coming from every angle, such as adverse inspection findings, processing and equipment issues, people issues. Going into a role at NSF where I can use these experiences to help other organizations will be very rewarding.

You joined NSF in March – what made you want to work for NSF?

I'd done all my QP modules with NSF and I've always being particularly impressed with the delivery of training and found the experience enjoyable. I'm the sort of person who likes variation, and this role allows me to see the industry in a different light moving into consultancy and training. I'm really looking forward to meeting new people and expanding my network.

What are you focusing on at NSF?

I'm focusing on the biotech side of things. However, I've worked in many disciplines – validation, engineering – even a bit of health and safety. Working in an operational role I have been involved in many troubleshooting scenarios, ensuring the root cause is determined and the appropriate, effective CAPAs put in place. I've also been involved in many inspections and have run programs of inspection readiness and remediation. All these experiences I look forward to using when working with our clients.

How do you see the future of biotech?

I think it's going to continue to innovate. We're going to see new therapies and new technologies come through. Obviously, we're seeing an increase in AI and automation, and it's important for NSF to keep ahead of the trends, so we can help clients as the industry innovates.

We're going to also see younger generations come through, linking back to my interest and passion for STEM, and people are going to want different levels of work-life balance, different ways of working and how people want to learn may change. I think it's going to be really interesting to see how we adapt as a training and consultancy business. We're seeing it now with COVID-19 with the move to virtual and remote services.

What do you enjoy doing outside of work?

Most of my time evolves around my seven-year old son, I dedicate my weekends to my family as I don't see them much through the week. Although I wouldn't claim to be the best chef, I do enjoy cooking and having family time around the table.

I'm based on the Cardigan Coast, near New Quay, in Wales and it's beautiful to get out and enjoy the fresh air on coastal walks and the stunning beaches.

Regulatory Update

Pharma EU News

by Pete Gough,
Vice President, Pharmaceuticals,
NSF International

Nitrosamine Contamination Risk Assessments Required for Biologic Medicines

A June 25 CHMP Assessment Report has recommended extending the requirement to conduct a risk assessment to consider the possibility of the presence of nitrosamine contamination to biological medicinal products. This requirement applies to both new marketing authorization applications and all existing products. The approach for risk evaluation/risk assessment should cover manufacturing processes of active substance and finished product in consideration of the root causes, and subsequent confirmatory testing in the finished product in case a risk is identified.

COVID-19 Pandemic Driven Changes

The EMA and the European national competent authorities have all issued guidance in response to the COVID-19 pandemic. Much of this guidance focuses on adaptations to the regulatory framework to address challenges arising from the pandemic, with a focus on crucial medicines for COVID-19 patients.

The EMA has a web page dedicated to COVID-19 guidance that covers:

- Early support for medicine and vaccine developers
- Accelerated procedures for COVID-19 treatments and vaccines
- Advice for sponsors and stakeholders involved in clinical trials for COVID-19 treatments and vaccines
- Advice for sponsors of clinical trials affected by the pandemic
- Guidance on regulatory expectations and flexibility (human medicines)
- Guidance on regulatory expectations and flexibility (veterinary medicines)

To reduce the risk of shortages or supply disruption from manufacturing and/or supply problems, the EMA has made an exceptional change management process (ECMP) available to marketing authorization holders of crucial medicines for treatment of COVID-19 patients. This ECMP permits the swift implementation of changes to suppliers and/or manufacturing/control sites necessary to reduce the risks of shortages under certain conditions intended to ensure the quality of the medicinal product, while deferring the full assessment of the variation.

The pandemic has also led to many deadline extensions:

- Comments on the draft of GMP Annex 1 moved to July 20, 2020
- The results of company's nitrosamine risk assessments moved to October 1, 2020
- The implementation of the Medical Devices Regulation extended by one year to May 26, 2021

EU Clinical Trial Regulation Implementation Date

At their virtual management board meeting on June 11, the EMA proposed December 2021 as the 'go-live' date for the Clinical Trials Information System (CTIS), which is the IT portal necessary for the operation of the Clinical Trial Regulation (CTR) 536/2014. The EMA has said that this would then also be the implementation date for the CTR.

Brexit

The UK and the EU are holding talks aimed at reaching a comprehensive trade agreement on their relationship from 2021 onward. These discussions have been disrupted by the COVID-19 pandemic and are now being conducted by video conferencing. The UK government refused to support an extension of the transition period beyond the end of 2020, so if

an agreement cannot be reached by the end of this year there remains the possibility of a no-deal exit.

ICH News

The ICH biannual meeting, scheduled to be held in Vancouver in May 2020, has been canceled due to the COVID-19 pandemic and resulting global travel restrictions. It is hoped that the meeting planned for mid-November 2020 in Athens, Greece, can still take place.

ICH Q3C(R8)

The Step 2b draft of Q3C(R8) was endorsed on March 25, 2020 and is being issued for public consultation in each ICH member country/region. This draft revision contains recommended permitted daily exposure (PDE) levels for three solvents: 2-methyltetrahydrofuran, cyclopentyl methyl ether and tert-butanol.

EU Implementation of Q12

On March 4, 2020 the EMA and the Commission issued a note on the implementation of Q12. In this note they state that *"additional scientific risk-based approaches to defining Established Conditions and associated reporting categories, as described in Chapter 3.2.3, and the Product Lifecycle Management (PLCM) Document, as described in Chapter 5, are not considered compatible with the existing EU legal framework on variations."*

The note goes on to emphasize that *"the legal framework always takes precedence over technical and scientific guidelines."* The note then states *"this means that the definition of Established Conditions and their reporting categories must follow the requirements laid down in the current EU Variations Regulation and associated EU Variations Guidelines. With respect to the PLCM document, in case such a document is submitted, it cannot be currently recognized in the EU due to the fact that it is not referred to in the EU legal framework."*

The note ends with the statement *"the tools and concepts in the ICH Q12 guideline that are not foreseen in the EU legal framework will be considered when this framework will be reviewed. In the meantime, the European Commission, together with the EMA and the National Competent Authorities, will continue to work on the implementation of the ICH Q12 guideline within the existing EU legal framework."*

So, where does this leave the EU with respect to the implementation of Q12? This question is not answered by the EMA/Commission note. It states that some of the tools and concepts in Q12 can already be applied within the EU framework but offers no solutions or timeframes for addressing the mismatches that the document highlights.

EU Medical Devices News

by Julian Thorns,
Managing Consultant, Medical Devices, NSF International

European Regulatory News and Regulation on Medical Devices (EU) 2017/745

Now it's official: the European Medical Device Regulation date of application was postponed for a year to enable medical device manufacturers and other economic operators to focus on withstanding the COVID-19 pandemic.

Under this scenario medical device manufacturers have gained more time but should not interrupt implementation and address strengthened requirements to be ready for the new EU MDR, but also upcoming changes and clarifications set by implementing acts or guidance.

Find out what the delay of Regulation (EU) 2017/745 means for manufacturers, including direct changes, what remains the same and other areas affected by the new deadline. Read NSF's white paper – MDR Compliance Postponed Until May 2021 – What You Can Do Now.

Biological Evaluation of Medical Devices – Assessment of Biocompatibility under ISO 10993-1:2018

With the introduction of the Regulation (EU) 2017/745 (MDR) in combination with the revision of the international standard ISO 10993-1 in 2018, the assessment of biological safety of medical devices is increasingly a focus of the notified bodies. In accordance with ISO 10993-1:2018, a risk-based approach in strong relation with ISO 14971 is required, as well as the documentation in a biological evaluation plan and report.

We summarized in a white paper how ISO 10993-1:2018 can be used as a tool to evaluate the biological safety of a medical device and how to structure the biological evaluation as a three-tiered approach.

Read the white paper – Biological Evaluation of Medical Devices – Assessment of Biocompatibility

Update of MDCG-Guidance 2019-3 – Interpretation of Article 54(2)b

The guidance document published in March 2019 on how to interpret the requirement in Article 54(2)b has been extended to include procedural aspects for applying for a product certification audit with the notified body.

Article 54 requires manufacturers of Class III implantable medical devices and active medical devices for the administration/removal of medicinal products from the body (Class IIb) to undergo a consultation procedure in connection with the clinical evaluation with a so-called "expert panel." There are exceptions to this obligation, one of which is misleadingly described in Article 54(2)b.

This guidance document attempts to dispel this misunderstanding by explaining why devices already placed on the market under a directive certificate are exempted from this obligation and what information must be provided to the notified body in this context.

New MDCG Documents for Clinical Evaluation

The European Commission has provided new guidance documents for manufacturers and notified bodies. These documents deal with clinical evaluation and post-market clinical follow-up (PMCF):

- MDCG 2020-5 Clinical Evaluation – Equivalence; a guide for manufacturers and notified bodies
- MDCG 2020-6 Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC; a guide for manufacturers and notified bodies
- MDCG 2020-7 Post-market clinical follow-up (PMCF) Plan Template; a guide for manufacturers and notified bodies
- MDCG 2020-8 Post-market clinical follow-up (PMCF) Evaluation Report Template; a guide for manufacturers and notified bodies

ISO 14971

The translation of ISO 14971 has been completed and nothing more stands in the way of the publication of DIN EN ISO 14971. In the national foreword of the standard, it is explicitly stated that the transition period will remain as planned.

This means that a corresponding adaptation of the deadline for adoption of the European standard EN ISO 14971:2019 to the postponement of the EU MDR is not planned for standardization reasons.

PINSIGHTS BY NSF

Have you seen NSF's EU MDR Notified Body Map?

This map displays which notified bodies have the scope to certify specific medical device products by NBOG code, country and conditions. Use the filters to identify the product codes that are within your portfolio and our tool will provide the notified bodies that are available for you. Similarly, you can select your existing notified body (if notified to EU MDR) and determine if it covers the scope of your product. **View here >>**

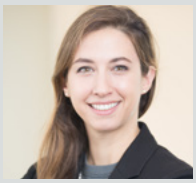
It is pointed out that the risk-benefit analysis described in Section 7.4 and the assessment of the overall residual risk specifically described in Section 8 provide the organization with the means to respond appropriately with its products to changing requirements or conditions.

Should you have any questions for the above-mentioned topics, or on our white papers, feel free to contact us at **info-medicaldevices@nsf.org**.

U.S. Medical Devices News

by Deborah Baker-Janis, Senior Director, Medical Devices, NSF International

& Caroline Rhim, Executive Director, Medical Devices, NSF International



& Meaghan Bailey, Executive Director, Medical Devices, NSF International

COVID-19

Read our concise COVID-19 regulatory update.

eSTAR (electronic Submission Template And Resource (eSTAR)) Pilot Program)[1]

On February 27, 2020, U.S. FDA announced a new pilot program, electronic Submission Template And Resource (eSTAR), to improve the 510(k) review process under MDUFA IV. Some notable elements of this program are:

- eSTAR utilizes a template similar in content to the template utilized by FDA reviewers
- eSTAR eliminates the need for a refuse to accept (RTA) checklist

FDA will evaluate whether the use of eSTAR (in comparison to e-submitter and e-copy) produces submissions with greater consistency and a more efficient review, thus allowing more timely access to safe and effective medical devices.

510(k) Third Party Review Program (3P510(k))

On March 12, 2020, FDA issued the final guidance "510(k) Third Party Review Program – Guidance for Industry, Food and Drug Administration Staff, and Third Party Review Organizations".[2] The 510(k) Third Party Review Program (Accredited Persons program) is a voluntary program, which allows accredited organizations to review 510(k) submissions for low- to moderate-risk devices. This guidance discusses: factors that the agency uses to determine whether devices requiring a 510(k) are eligible for third party review; processes for third party reviewers to follow in order to reduce substantive FDA re-review; requirements and process for accreditation/re-accreditation of review organizations; and the ability of review groups to leverage the International Medical Device Regulators Forum (IMDRF) compliant documentation.

E-Copy Program

On April 27, 2020, FDA issued an updated guidance "eCopy Program for Medical Device Submissions – Guidance for Industry and Food and Drug Administration Staff."[3] Due to the COVID-19 pandemic and the expediency with which FDA is reviewing submissions, FDA added another submission filing mechanism to the guidance (submission by email) specific to Emergency Use Authorization (EUA) requests. This revision closely follows the December 2019 revision of the guidance, which eliminated the need for multiple submission copies, including a paper copy.

Notable Approvals and Clearances

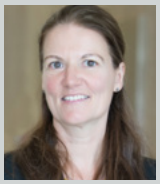
In addition to numerous emergency use authorizations to address the COVID-19 pandemic, the following de novo authorizations, PMA approvals, and 510(k) clearances, issued in the first half of 2020, were notable:

- Philips Medical Systems, BX100 biosensor – 510(k) clearance for wearable sensor for tracking patient's physiological data and contextual parameters in a hospital environment
- 4-D Medical, XV Technology – 510(k) clearance for 4-D imaging software for the diagnosis of lung impairment

- Qiagen, therascreen® BRAF V600E RGQ PCR Kit – PMA approval for real-time PCR test for the detection of gene mutations in colorectal cancer tissue
- Intact Vascular, Inc., Tack Endovascular System® – PMA approval for arterial repair device following percutaneous transluminal balloon angioplasty (PTA) dissection
- Roche Tissue Diagnostics, CINtec PLUS Cytology Test – PMA approval for immunocytochemical assay for women with human papillomavirus (HPV) to identify risk of cancer
- Contura International, Bulkamid Urethral Bulking System – PMA approval for urethral injection for the treatment of stress urinary incontinence (SUI)
- Bay Labs, Inc., Caption Guidance software – de novo authorization for cardiac 2-D ultrasound image acquisition software
- Bluegrass Vascular Technologies, Inc., Surfacer Inside-Out Access System – de novo authorization for reverse central venous recanalization system for kidney dialysis
- Asuragen, AmplideX Fragile X Dx – de novo authorization for the first diagnostic test for Fragile X
- Hyperfine Research, Inc., Lucy Point-of-Care Magnetic Resonance Imaging Device – 510(k) clearance for first bedside MRI system
- VivaLNK, VivalNK platform – 510(k) clearance for continuous ECG with wearable sensors and SDK

[1] www.fda.gov/medical-devices/premarket-notification-510k/510k-program-pilots
[2] www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-third-party-review-program
[3] www.fda.gov/media/83522/download

Pharma U.S. News



by Marinka Tellier,
Director of Regulatory Affairs,
Pharmaceuticals,
NSF International

U.S. Regulatory Preparedness in Facing the COVID-19 Pandemic

History of Framework

A major contributor to regulatory preparedness during a public health crisis came into place with the establishment of the Emergency Use Act in 2004, as part of Project Bioshield, which amended the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. It was understood that the regular framework in place to review, approve and oversee therapeutics products would not be adequate during a crisis, in part due to the regular time frame needed to review and approve therapeutics which could result in unacceptable delays. An alternate mechanism was created allowing for more regulatory discretion while keeping enough oversight in view of a changed risk/benefit profile. This led to the creation of the Emergency Use Act in 2004 which was further amended by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA), the 21st Century Cures Act of 2016, and finalized in 2017 (Public Law 115-92).[1]

Under this act there is a requirement for the provision of effective assistance to State and local government and a provision for capacity to respond in the event of a public health emergency (including bioterrorism). This includes capacities for the following: (1) effective public health surveillance and reporting mechanisms at the State and local levels; (2) appropriate laboratory readiness; (3) properly trained and equipped emergency response, public health, and medical personnel; (4) health and safety protection of workers responding to such an emergency; (5) public health agencies that are prepared to coordinate health services (including mental health services) during and after such emergencies; and (6) participation in communications networks that can effectively disseminate relevant information in a timely and secure manner to appropriate public and private entities and to the public.

Statutory Requirement

Further, under the Emergency Use Act, the FDA Commissioner may allow unapproved medical

products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN (chemical, biological, radioactive, or nuclear) threat agents when there are no adequate, approved, and available alternatives. FDA may issue an Emergency Use Authorization (EUA) when the following four statutory criteria are met:

1. The agent referred to in the declaration can cause serious or life-threatening disease or condition.
2. Evidence of effectiveness based on the totality of scientific evidence available.
3. The known potential benefits outweigh the known potential risks.
4. There is no adequate, approved, and available alternative (this may include shortage due to insufficient supplies of approved products).

In addition, FDA may allow emergency dispensing (including mass dispensing at a point of dispensing) of approved medical counter measures (MCM) during an actual CBRN emergency, without requiring an individual prescription for each recipient of the MCM, if (1) permitted by state law or (2) in accordance with an order issued by FDA. It also may include waivers of cGMP requirements, when appropriate to accommodate emergency response needs (e.g. storage or handling).

Prior Use of EUA

Prior to the declaration of the COVID-19 pandemic, EUAs were limited to those issued for the treatment of inhalation anthrax following an outbreak in a postal facility, and those issued in 2009 in response to the H1N1 Influenza outbreak which included EUAs for antiviral medications, in vitro diagnostics and N95 respirators, and more recently for diagnostic test for MERS corona virus (2013), Ebola (2014) and Zika virus (2016).[2]

Current Use of EUA

During the current COVID-19 pandemic the EUA has been applied for various medical counter measures including many diagnostics. As of July 2020, FDA reports it has worked with more than 400 diagnostic test developers and issued 182 EUAs of which 29 are for antibody test and two for an antigen test. To further aide in obtaining EUA and expanding diagnostic capabilities, the FDA issued a Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency[3] which includes EUA submission templates for molecular, antigen, and serology tests to streamline EUA request. Other examples of EUAs issued include those for personal protective gear, modified use of anesthesia gas machines for use as ventilators, etc. and notably the EUA for use of Remdesivir, a drug initially developed as a therapeutic for Ebola, to treat patients hospitalized with COVID-19.

FDA Communication – Daily Roundup

Another important part of preparedness and response during a crisis is communications. As of April 2020, FDA has been posting daily updates on its entry webpage summarizing the many activities related to the response. In addition, it has offered more than 50 new guidances related to COVID-19 covering a wide range of topics.

In the wake of the current pandemic, it is anticipated that new regulatory legislation will be developed to address regulatory preparedness for future health crisis where the current regulatory framework lacked. For example, the most effective way for ensuring timely availability of diagnostic capabilities may need to be re-assessed to assure availability of tests that have met a minimum set of validation criteria. Also, where FDA is responsible for protecting the health of all Americans a stark disparity in health outcomes has become evident with certain populations disproportionately hit by the epidemic. This calls for enhanced communications to at-risk populations and having a regulatory framework in place that ensures access to medical treatment for those most affected and adequate representation in clinical trial evaluations. Lastly, if a vaccine were to become available with limited initial supply a framework under which to triage may be needed to maximize the benefit in protecting public health.

[1] Emergency Use Authorization of Medical Products and Related Authorities; Guidance for Industry and Other Stakeholders; Availability www.federalregister.gov/documents/2017/01/13/2017-00721/emergency-use-authorization-of-medical-products-and-related-authorities-guidance-for-industry-and-related authorities

[2] Emergency Use Authorizations for Medical Devices www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations

[3] FDA Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-coronavirus-disease-2019-tests-during-public-health-emergency-revised

News From NSF...

NSF INTERNATIONAL'S HEALTH SCIENCES TEAM JOINED FIGHT TO SAVE LIVES WITH MORE VENTILATORS

NSF International's Senior Director of Health Sciences James Pink has supported both medical device manufacturers and industries not usually involved in medical devices such as automotive, aerospace, defense and consumer electronics to rapidly scale up the manufacture of life-sustaining oxygen ventilators.

As part of a government industry liaison initiative, James has been on-site at various locations across the UK. His support includes advice on product safety, regulatory compliance and the quality systems requirements necessary for the emergency use authorization to place rapidly manufactured ventilators into the National Health Service.

Read the full news item >>

Amarex, an NSF International Company, Executed Five Rush COVID-19 Related Submissions to the FDA

In March 2020, Amarex Clinical Research worked tirelessly to support the COVID-19 response efforts. They executed and submitted to the U.S. FDA, five emergency use authorizations of clinical development products to treat COVID-19. Included, were rushed IND, IND Amendment and Compassionate Use Approval (CUA) applications for CytoDyn's monoclonal antibody product, Leronlimab, for emergency treatment of COVID-19 patients.

Amarex also completed a rush submission to the U.S. FDA for a CUA for treatment of COVID-19 patients with a device currently in testing under an IDE for a different medical condition. Finally, they executed a rush submission to the U.S. FDA of an EUA for a PCR-based IVD for the rapid detection of the coronavirus (SARS-CoV-2).

Since this initial rush of applications in March, Amarex has continued submitting multiple other COVID-19-related project applications both nationally and internationally.

Read the full news item >>

AMAREX
an NSF International Company

Protecting and Improving Human Health – Together

NSF International's Executive Director of Medical Devices and IVDs Robyn Meurant has been instrumental in the global life-saving effort by establishing crucial connections between UK ventilator manufacturers and the World Health Organization, including the department associated with local production of needed health products. The devices offer resource-limited countries the real possibility of manufacturing their own ventilators as an alternative to expensive, highly engineered solutions.

Read the full news item >>

NSF International's New Checked by NSF™ Program Helps Businesses Reopen and Stay Open Safely

Since the onset of the COVID-19 pandemic, restaurants, hotels, retail stores, museums and airlines across the globe have asked NSF for advice and assistance with their plans to reopen in the face of COVID-19. NSF quickly responded by developing "Checked by NSF," an assurance program that helps organizations build trust with staff, customers and the community by helping address the uncertainties of planning for the new normal of a COVID-19 world.

Read the full news item >>

Advice to the UK Regulator

Robyn Meurant has been seconded as an IVD expert advisor to the UK regulator MHRA. In this role she has provided expert advice to the agency on the types of IVDs needed to support the different diagnostic use cases that are mobilized in the response to the pandemic. Diagnostic use cases may include surveillance and past exposure, to name a few. Each can have a different utility in providing valuable information during the pandemic (see more on diagnostic use cases). Tests meant for one application can be of quite limited use in another application, whilst others may be more broadly useful in a variety of settings. It is important to understand how tests should be designed to meet a use case, and what associated validation by the manufacturer is expected.

Mapping the Global Molecular Diagnostics Industry and the Changing Regulatory Landscape

Robyn Meurant has also been working with the University of Cambridge to build a database to track the development of molecular IVDs (PCR etc) related to COVID-19. This work has evolved from related activities undertaken by the University as part of the European Research Council-funded CANCERSCREEN project. The CANCERSCREEN* research team is led by Dr. Stuart Hogarth at the Department of Sociology, University of Cambridge who has mapped the global molecular diagnostics industry in relation to cancer screening and the changing regulatory landscape.

Leveraging this database, the team has gathered data on over 320 molecular diagnostics firms that are producing/developing tests for COVID-19. This is a fast-moving field and data collection remains a work-in-progress. This database is open access and has utility for laboratories needing to understand more about the development and regulation of any particular molecular IVD. Access the database of COVID-19 molecular diagnostics firms, and the first blog post analyzing the data.

Face Masks and More!

During April and May 2020, more and more problems occurred with defective face masks and led to official product alerts and recalls. NSF initiated a Masks and More competence team to support our customers in all divisions to prevent risks connected to the procurement and use of face masks. Masks and More is a cross divisional team from Health Sciences, Food, Labs, Agriculture and Water. The first topic is the support regarding the manufacturing, distribution and correct wearing of face masks and other protective equipment. Within this team we can quickly identify a responsible person within NSF for all mask-related customer demands to give our customers the best support during this ongoing crisis and in the time beyond.

Useful resources can be found using the links below

Webinar: Make Hand Sanitizer, Not Mistakes: Understand the FDA Policy
by Maxine Fritz

Webinar: Reopening Your Business and the Use of Face Masks
by Kim Trautman

UPCOMING SPEAKING/EXHIBITING EVENTS

- **2020 ISPE Europe Annual Virtual Conference**
  September 16-17
- **MedTech Summit 2020: EU MDR & IVDR – Virtual**
  October 12-16
- **"Successful Implementation of Regulation (EU) 2017/745 in Practice" NSF Symposium Event**
  Hamburg, Germany | September 17-18

Ready to Deliver NSF Virtual Training!

Catherine Kay and Peter Gough ready in their virtual classrooms to deliver our first-ever virtual QP course on pharmaceutical quality systems. This included breakout rooms, interactive whiteboards, annotation tools and more.

Update on Martin's 6/60/600 Challenge

As many of you may remember, Martin was preparing to compete in a major endurance challenge to celebrate turning 60. This involved swimming 6 miles, running 60 and cycling 600. Unfortunately, organizers postponed the event until next year. Although he is really disappointed, his body is somewhat relieved. We will keep you posted!

Forthcoming Courses

Virtual, Instructor-Led Pharma and Medical Device Courses, August to September 2020

We're offering our full suite of courses through scheduled virtual classrooms. Courses can be booked online and via our NSF Pharma and NSF IVD apps.

Equipment, Facilities and Utilities Qualification
– Bitesize Two-Hour Course
August 5 | Course Fee: £195

Pharmaceutical Quality Systems
August 10-13 | Course Fee: £2,800

European Medical Device Regulation (EU MDR) Internal Auditor
August 11-13 | Course Fee: $1,599

Cleaning Validation
– Bitesize Two-Hour Course
August 12 | Course Fee: £195

Pharmaceutical Microbiology
August 17-20 | Course Fee: £2,800

Process Validation
– Bitesize Two-Hour Course
August 19 | Course Fee: £195

An Update on Annex 1 & How to Develop an Effective Contamination Control Strategy
August 20 | Course Fee: £700

ISO 14971:2019 Application of Risk Management to Medical Devices
August 25-26 | Course Fee: $1,200

Virtual and Desktop Auditing
August 25 | Course Fee: £700

Analytical Validation
– Bitesize Two-Hour Course
August 26 | Course Fee: £195

Data Integrity
August 27 | Course Fee: £800

Deviation and CAPA Management
September 8 | Course Fee: £700

Human Error Prevention
September 9-10 | Course Fee: £1,400

ISO 14971:2019 Application of Risk Management to Medical Devices
September 16-17 | Course Fee: $1,200

Mathematics and Statistics
September 21-24 | Course Fee: £2,800

Supplier Management
September 23 – 24 | Course Fee: £1,400

Pharmaceutical Legislation Update
September 29 | Course Fee: £700

European In Vitro Diagnostic Regulation (EU IVDR) Internal Auditor
September 29-30 | Course Fee: $1,600

Regulatory Affairs for QA: Marketing Authorisations
September 30 | Course Fee: £700

Click here for more information or to book our pharmaceutical courses

Click here for more information or to book our medical device courses

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

Success Stories

Remote Coaching of SMEs Prior to a Regulatory Inspection

by Lynne Byers,
Vice President, Pharmaceuticals, NSF International

Regulatory inspections can be nerve-racking for those who have not previously presented to an inspector. NSF performed coaching of a company's subject matter experts (SMEs) prior to planned U.S. FDA and Health Canada inspections. We used a remote approach which was more cost-effective than having consultants visit the site and we could use a wide variety of NSF's SMEs. For sterility assurance topics we used one of our microbiologists, for validation topics our validation experts, etc. This provided a greater challenge to the company SMEs than just using one or two of our consultants and helped to provide more in-depth questioning around the topic. By using video-conferencing tools it is easy to assess softer skills like eye contact and clarity of answers. Following each session, we gave feedback both verbally and in writing about how to improve the presentation of the information. If required, we planned a further session with the SME to give them the opportunity to improve and build confidence. As the work was performed remotely, it was easier to schedule an additional session at a time suited to both parties.

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