ESSENTIAL RULES WHEN INVESTIGATING GMP DEVIATIONS DURING STERILE PROCESSING

by John Johnson

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

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

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

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

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

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

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

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

WHAT ARE THE KEY ATTRIBUTES OF A STERILE PRODUCT?

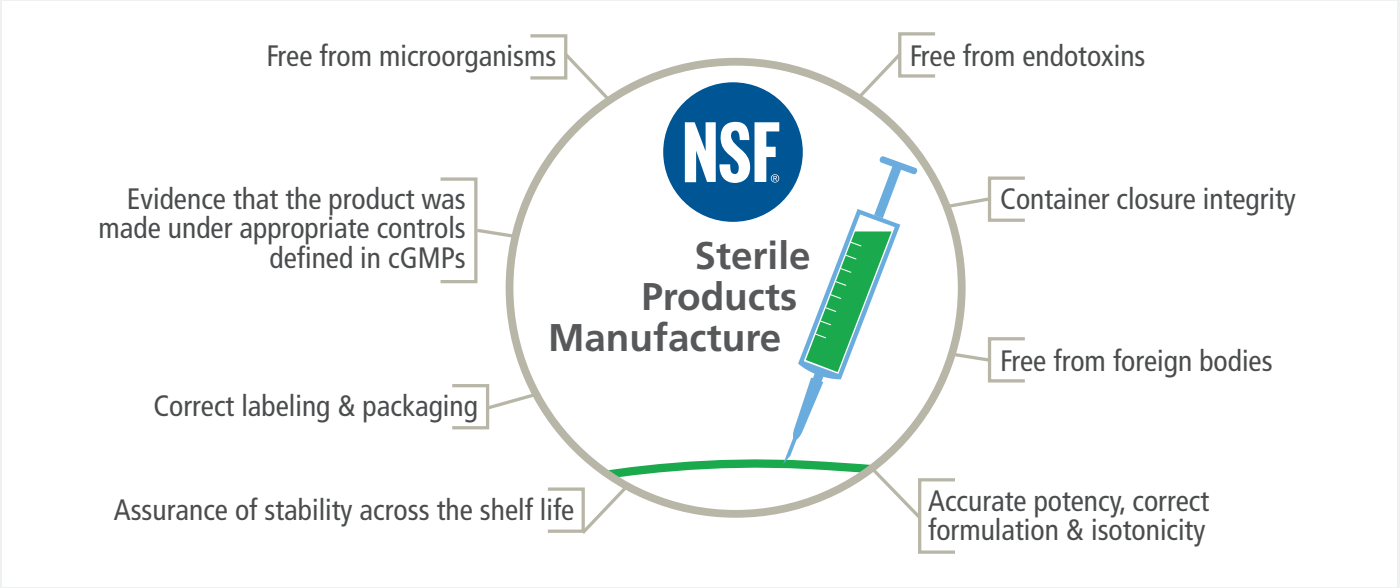

Figure 1.

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

Always remember that making sterile products is dependent on a multitude of details that are dependent on effective design, good controls and stringent monitoring. When Sir David Brailsford set out to transform the success of the Great Britain Olympic cycling team, he knew that there was no silver bullet for success and that almost imperceptible improvements across an infinite number of controls would be the way to dominate the sport. In the same way, making sterile products demands an attention to detail across all disciplines and a passion to flawlessly execute processes each and every time. More than that, it requires us to continually examine the pressures and risks in the process and eliminate those fleeting undetected issues that can lead to product contamination and patient harm.

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

So what are the best practices in dealing with variation?

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

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

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

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THE KEY MESSAGE HERE IS:

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

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

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

FIVE TO THRIVE		
Key process	**Measure or evidence**	**How could this be used in a deviation associated with sterile processing?**
Immediate engagement	All issues are logged and triaged within one shift, evidenced by real-time logging.	An issue occurs. Staff members are trained to notice it. They don't pass it by. They are educated to be alert to the problem. They log it and know how to escalate the problem as their training was based on case studies. The investigation begins immediately before the trail goes cold.
Gemba	A "crash team" is engaged to go to the place of the issue and support its resolution.	A team of respected subject matter experts is available to support the operational team when exceptional events occur. They are highly expert, open minded and well drilled. In sterile processing, this may include expertise in microbiology, cleanrooms, sterilization, disinfection, gowning and aseptic behaviors.
Triaging using a documented risk assessment	A pro forma is used to assess risk, completed at the time of the gemba within one shift of the occurrence.	The pro forma is used to assess risk leading to an effective correction, e.g. terminating the aseptic fill operation immediately, continuing once measures are taken or recording as an observed risk. The right people are there to make this decision, accessing the right information and recording their assessment with scientific rigor. In steriles manufacturing, it is impossible to make an accurate risk assessment from a meeting room, days after the event.
Klein process to determine potential root causes	Staff are trained in timely and thorough processes for investigation. Blame free culture allows investigations to be conducted accurately without recrimination.	Staff members use the five whys, Ishikawa, the six Ps, is/is not/ maybe, RAPID decision making, FMEA, etc. to bring the issue to the surface. They are trained in sensitive, open-minded, blame-free investigations where words and actions are critical to transparency and objectivity. In steriles manufacturing, a holistic approach to how sterility is assured is critical and will depend on a multidisciplinary approach by staff who work well together to piece together the chain of events that led to the risk.

Key process	Measure or evidence	How could this be used in a deviation associated with sterile processing?
Document in real time using an investigation worksheet	Investigations are completed at a rate dependent on their risk; the 30-day, one-size-fits-all expectation isn't often appropriate to high-risk events.	The pro forma is used as a trigger to ensure the right risk-based decision making tool is used for each situation. It also records any observations and immediate corrections ("make safe"). The tools (from ICH Q9 and NSF best practices) are used to structure the investigation and ensure no evidence is missed at the time. The pro forma is the first part of the deviation investigation report and records the product impact assessment, assessment of risk to the facility and any impacts on the product quality attributes. It also records the facts and decisions made during the investigation. In steriles manufacturing, it is often impossible to identify the right course of action from a meeting room, days after the event. Investigations need to be thorough and timely; not hampered by a lack of resources.

FOR MORE INFORMATION:

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

ABOUT THE AUTHOR

John Johnson is passionate about helping organizations foresee and overcome the barriers to sustainable long-term growth. He brings 28 years' experience across a range of companies in the pharmaceutical and healthcare industry. He has worked in small, medium and large pharma biotech companies across the product lifecycle for a wide range of dosage forms, holding senior operational and corporate-level experience in operations and quality assurance and leading multinational companies in many strategic projects.

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