WHY ANNEX 1 IS IMPORTANT TO YOU

by John Johnson

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

> Why is the regulation being changed?

> How will it affect my operation or the company as a whole?

> Does the revision give a signal to a change in perspective within EMA?

> Does the revision give some clues on how the changes will be monitored and enforced?

> What do I need to do to keep in-step with these changes, regardless of the dosage form I work within?

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

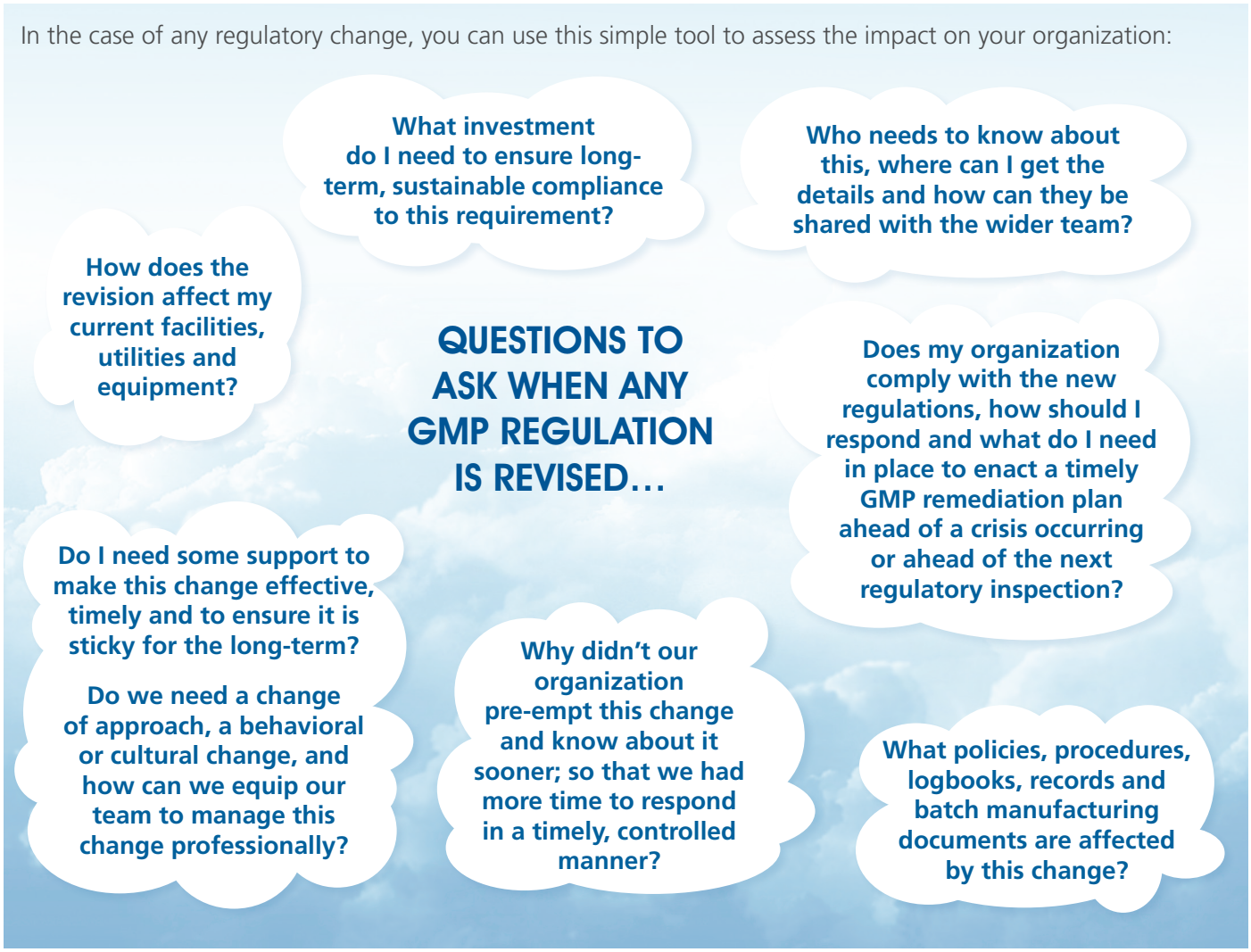
Whilst Annex 1 is focused on sterile production, the proposed clarifications and the changes to be made will have a definite knock-on impact on how the regulators regulate and how the industry designs, operates and checks the effectiveness of the whole Pharmaceutical Quality System (PQS).

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

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

Key reasons for revision to Annex 1	What should I be asking myself, regardless of the dosage form I am responsible for?
3. The authorities' unique view of the industry is troubling them. They are seeing recurring GMP deficiencies, basic defaults against the regulations, inadequate root cause analysis and ineffective CAPA. They are seeing poor deployment of ICH Q9 Quality Risk Management and issues concerning sterility assurance are not diminishing, causing recalls and product shortages. In short, when trust is eroded, there is a greater need for verification and enforcement.	- Does my PQS have a clear risk management process that leads to a risk register, acted on via quality objectives year after year? - Does my product impact assessment process tend to justify unsound, unscientific or bad practice, often just to seek a way of continuing to supply product without addressing the root causes? - Am I noticing recurring issues? Am I visually active in seeking transformational change in the severity and frequency of recurrence?
4. The authorities have noted a trend in fragmentation of supply chains leading to the diffusion of QA oversight and responsibility. Sterile products are often made in locations and by companies without a long-compliance history in this field with low level understanding of the technologies and risks. This is evidenced by the prevalence of basic GMP deficiencies noted on-site during regulatory inspections. As a consequence, Annex 1 needed to be made less ambiguous with less room for interpretation.	- How do my EU Qualified Persons oversee the supply chain as required by Annex 16, and how is this documented? - How well does my vendor approval system work and do I have any special cases where a person-in-plant is needed to guide, mentor and verify the performance of our contractor? - Do my manufacturing partners operate a quality system that meets ICH Q10 and is clearly used in day-to-day operations?
5. After the global recession 10 years ago, many firms slashed their training budgets and downsized the way they educate their staff and develop their managers. It is now evident that some critical position holders may have the "know-how" but not the "know-why". Hence the trend in sterile inspections for poor decision making, inadequately completed investigation reports and acceptance of repeat, low level issues – often first noticed during the regulatory inspection. More detail is needed in Annex 1 to provide clearer guidance and direction.	- Of course we train our staff, but do we educate them so that they can make the right calls at the right time? Are our training programs developing the subject matter experts of the future? - Do we have a successor program, do we define "station manning" to allow people to shadow managers, internal audits and key meetings so that they learn the role as part of their daily job? - How do we check that the training has been absorbed and best practice is implemented? - How do we deal with those who just don't get it?

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



For more information:

> Visit our resource library (**www.nsf.org/info/pblibrary**) and watch the webinar EudraLex Vol IV Annex 1 – How Will It Affect You

> Whether you are a steriles manufacturer or not, take some time to formulate a plan of action because, subtly but surely, your EU regulator is telling you:

- Better regulation is needed as many sectors of the industry are clearly struggling to comply with the basic requirements of GMP
- Product shortages, recalls and regulatory censure are very troubling to the authorities, and demonstrate that changes across the industry in the last 10-15 years are not visibly improving the quality or safety of products manufactured or supplied in and to global markets
- Recurring GMP deviations and deficiencies against the GMP regulations demonstrate a lack of effective root cause analysis, a lack of rigor in identifying the right CAPA and an acceptance of variation that can lead to significant impact on product quality

- Though a quality system (underpinned by a robust staff education program) is a mandatory requirement, it will not deliver the required level of quality assurance without the engagement of staff at all levels. This engagement is needed before the right communications, behaviors, culture and mindset can be put in place. The regulators are noting elegant quality systems across our industry but likewise they see products of variable quality and often made to inconsistent or inappropriate levels of GMP

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

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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