Editor's Message

Annex 1 Changes Effective in March

Many of the new provisions in the revised Annex 1 go into effect in 2009, so the *PDA Letter* starts the New Year off with two articles on the regulation. The cover story, by PDA's **Jim Lyda,** summarizes a meeting PDA sponsored in cooperation with PIC/S on Annex 1 implementation and risk management. As Jim relates, the meeting was very successful in generating dialogue between the inspectors and industry representatives in attendance. Out of respect to the attendees who were promised an environment for open discussion, the article does not include specific quotes from the various discussion segments of the meeting. A participant in the meeting, **Martyn Becker,** submitted the second feature article on Annex 1—a commentary on implementation strategies. Martyn believes many firms are right on top of the new provisions in the Annex, so they will not need to change much by due date in March. However, he outlines three specific areas of the document that firms might need to do some last minute adjustments in order to be in compliance.

Annex 1 and how it fits in with existing regulatory guidances worldwide is an important subject for most PDA members. It is clear from Jim's article that the EMEA intends to continue the dialogue with industry as the new rules come into effect. Martyn points out that the "biggest single" change in the document pertains to capping, which does not become effective until March 2010. I encourage readers to contact me if they have comments about the feature articles or if they would like to contribute to the dialogue in a future issue.

With the New Year underway, PDA welcomes new members to our volunteer Board of Directors. Our "News & Notes" announcement about the new BoD includes photos and brief bio information of the new members.

The "Science & Technology Snapshot" opens the year with a message from PDA Sr. VP **Rich Levy,** PhD, on the Associations 2008 accomplishments in Science and Technology. The "Quality & Regulatory Snapshot" also includes a 2008 retrospective from PDA VP **Bob Dana.**

Correction: Finally, we would like to apologize to **Miguel Montalvo.** In the October issue of the Letter, we incorrectly stated that he was the President of PDA's Puerto Rico Chapter; he is a Member-at-Large.

PDA Letter

Volume XLV • Issue #1 | **January 2009**

The PDA Letter is published 10 times per year, exclusively for PDA members.

Subscriptions are not available.

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Implementation Strategies for EU GMP Annex 1

Martyn Becker, Martyn Becker and Associates

In February 2008, EU GMP Annex 1 was republished in revised form. There were improvements, including some harmonization with the U.S. FDA guidance and some realignment of the 5 micron particle per cubic meter figure with ISO 14644. By now, industry has had plenty of time to consider EU GMP Annex 1, yet many firms might still be sorting out what is new and what is unexpected.

Although published in February 2008, many of the changes do not come into effect until March 2009, now only two months away, with the capping requirements being delayed until March 2010. Do we really need implementation strategies beyond those employed with previous versions of the annex?

Some Annex 1 requirements have been present from its first publication in 1989, e.g., the 5 micron requirement, redundant filtration, A-D grading system, and steam sterilization time/temperature/pressure relationship. These should have been rationalized, justified and/or implemented by industry for almost twenty years. Some of the newly-added items are straightforward enough to be "no-brainers" for those who have been keeping their eyes on the regulatory climate over the last decade or so, for the signs for their formal requirement have all been there. Examples of these are isokinetic probes for particulate monitoring (many companies have already been using them for years) and the per-batch pre-sterilization bioburden for terminal sterilization and sterile filtration, which was mandated by the EU Committee for Proprietary Medicinal Products in 1996. Anyone paying attention to these things has already been invested in implementing this. The process simulation requirements have been harmonized with the sensible requirements in the U.S. FDA aseptic processing guidance, which were generated through the highly-successful FDA/industry collaborative Product Quality Research Institute (PQRI) process in 2003. **[Editor's Note:** For more on the PQRI/FDA collaboration and PDA's role in the process, see the July/August 2005 *PDA Letter.*] There should be no issues there since harmonization is indeed what the industry has sought for years.

Some implementation strategies are indeed necessary simply because some of the changes require a different way of thinking. The following are three areas of the guidance that have either been amplified by the revision or are completely new, and, as such, firms should carefully consider how they impact their current practices:

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Qualification/Classification Requirements

Clean rooms are expected to be classified in accordance with ISO 14644-1 "Clean rooms and associated controlled environments—classification of air cleanliness," and the process of classification should be clearly segregated from routine monitoring, which makes sense and is here clearer than previous iterations of the annex. The number of locations is identified by the calculation in ISO 14644-1 as is the preferred method of sampling, so that the requirement is clear. Industry has been moving to the use of this classification logic over the last decade so that the implementation strategy, if not already in place, should be based on this process.

Routine Particulate Monitoring Requirements

Here we see a requirement for a formal risk management strategy with regard to monitoring locations linked to the locations used for classification. We also see a statement that is not initially clear in its intent: "[f]or Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly [...]." Does this mean that routine, regular samples should be taken over the duration of, say, an operational shift, as was the case with the stated interpretation of the word "continuous" in the 2003 edition of the annex? The requirement continues "[t]he Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded [...]."

This can surely only mean truly second-by-second continuous monitoring, since how else could you capture all interventions and transient events? How do we strategize for this, and is it even necessary?

To be sure, truly continuous critical location monitoring needs to be evaluated using a different rationale than the one used for the evaluation of point-in-time samples such as the ones that have been common with the use of turret-type manifold systems. With truly continuous

monitoring, out-of-acceptable-range spikes will certainly be detected. Finding such a spike with discrete samples was one thing, since an investigation would no doubt be triggered. Here however, the focus should be much more on accumulated data translated into process information regarding the state of environmental control at that sample point. So trend evaluations become more important than knee-jerk reactions to single spikes, since a single non-repeated spike may not mean that there is actually anything amiss.

While continuous monitoring at critical locations (say, close to the fill head) might perhaps provide a more complete picture of environmental conditions at that point, we need to understand the context. Why? Even truly continuous monitoring is still a sampling process, and simple mathematics will identify the tiny proportion of the environment that you are actually sampling. It is therefore important to apply an appropriate rationale to this, because the obtained results define only what is in the sample, not what is in the Grade A environment as a whole, in the same way that a process simulation using growth medium only gives absolute assurance for that particular fill (not for every fill) even though it is used to impart a level of assurance to the whole. The evaluation strategy should take this into account, alongside the operational limitations of the sampling equipment in terms of background noise and so on. Procedures should therefore be established and documented to guard against over-reaction to individual events, to evaluate trends in real time and to be able to detect drift from the defined state of environmental control.

Capping Environment

In this author's opinion, the biggest single issue to come out of the new edition of the annex was vial capping, with opposing EU regulatory views leading to the final wording being something of a compromise between two extremes. One regulatory opinion indicated that capping was required to be undertaken within a Grade A/B aseptic area with no exceptions, while others took the perspective that it was unnecessary and that the annex should not be published with that specific requirement as the only way to achieve the end. The compromise text therefore allows for application of sterile caps in aseptic Grade A/B, or alternatively as a clean process under a "Grade A air supply."

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The text in clauses 116 to 124 references the kind of unsupported statement that industry is constantly criticized for: "The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial..." (Clause 118). While this is a backstop risk-averse position, it does not take into account the kind of process challenge that is routinely carried out in industry, such as the microbiological container closure integrity challenge. If the closure is specified as being closed and integral without a crimped cap in place, then it must be up to the individual company to demonstrate by means of closure integrity validation of the un-capped container that this is actually the case. Arguments are made for the sealing ability of stoppers and vial necks without caps, and this is the way to demonstrate that it all works as stated. A benefit of undertaking this process is that it challenges not only the stoppering but also the potential for raised or misaligned stoppers that may or may not be detected by the raised stopper detector, which has been one regulatory argument for the statement above.

There are, of course, two potential outcomes to this kind of challenge process:

1. It passes, meaning that the containers can indeed be regarded as sealed.
2. It fails, and the company has to accept that the statement in clause 118 actually holds true in that case.

For the first outcome, there would perhaps be no need for either capping under aseptic conditions or maintenance under a "Grade A air supply" following exit from the aseptic area while in the latter case, protection would be necessary using either of the options listed. The implementation strategy would therefore benefit from inclusion of a container closure integrity evaluation process in order to determine which route should be pursued. This integrity process must be fully rationalized and documented on a scientific basis using realistic methodologies and acceptance criteria. If uncapped integrity can be confirmed then the way forward is simpler than if it cannot. If it cannot be confirmed then a decision should be made on how the units should be protected up to the point of capping.

Studies have been undertaken within industry (and supplied to the EMEA Inspectors' Working Group during feedback prior to publication of the Annex 1 update) that demonstrate the effectiveness and risk-averse nature of capping outside the aseptic processing area. If the decision is therefore taken to cap as a clean process outside the aseptic core in the absence of a clear indication of what a "Grade A air supply" means, further rationalization will need to be made concerning the actual required environmental conditions. If "Grade A air supply" means the full Grade A requirements as normally operated within an aseptic core, then there would be no difference in expectation—and such a workstation located outside an aseptic

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expectations because of the environment and potential interventions.

A critical part of operational design, therefore, needs to be the engineering-out of mechanical issues. For example, locating the capper as close as is possible to the aseptic out-feed and installing screw-feeders rather than conveyor belts to route the units into the capper, which would mitigate the risk of units falling over. There is a potential complication here since a raised stopper detector is normally located between the aseptic out-feed and the capper. One needs to consider which route is of lesser risk-minimal track distance post-out-feed but no raised stopper detector, or longer track including the detector? It may be that the value of the detector might be outweighed by the benefit of the short track and the potential for nonintervention by operators, which might lead to a reduced potential for contamination—but this would need to be rationalized and justified on a case-by-case basis.

If the track length is minimized, a screw feeder is implemented and the detector option not used, then there is minimal necessity for personnel intervention so that it may be possible to rationalize and risk assess the location of the capping process into a controlled, but formally unclassified area. If the detector is in place and therefore a longer feed track, there is increased potential for human intervention so that it may be necessary to place it in a formally classified area such as Grade D. Once decided, it is then perhaps a case of deciding what aspects of a genuine Grade A environment would be appropriate to be monitored. Then again, High Efficiency Particulate Air (HEPA) coverage of a connecting track is one thing, but is it possible to apply the same environmental criteria to a connecting tunnel as you would to the environment within the capper, where the crimping mechanisms are liberating aluminium particles? That would seem counter-intuitive. The air emerging from the HEPA filter should of course be of the same standard as that emerging within a unidirectional aseptic background in both cases; the difference lies in the background into which it is emerging and this should feature in the determination of which background and limits are most appropriate. The EU regulators themselves do not appear to be harmonized regarding what a "Grade A air supply" means in practice, and so a logical, scientific and justifiable approach is required to not only understand the key potential contaminants at this point of the process, but also to implement appropriate conditions and acceptance criteria that make the monitoring process truly value-adding in terms of sterility assurance.

Industry-Regulatory Dialogue Important

Product sterility is all about probabilities: the probability of a non-sterile unit existing in the environment in the first place, plus the probabilities of being able to detect and then locate it. Regulators and industry are ultimately aiming at the same target, which is the safety, protection, health and well-being of the patient and it makes sense to apply real and meaningful criteria to the assessment of our processing environments so that we do not head up the GMP spiral just for the sake of it. This is why it is so important for regulators and industry to be able to talk together in a reasonable manner and discuss the science and logic of how we should approach the manufacture of products purporting to be sterile.

In reality, neither side of the fence has the monopoly on knowledge and expertise in this area

In reality, neither side of the fence has the monopoly on knowledge and expertise in this area, regardless of how much one or the other side might think it does. In Europe, we could do far worse than take a leaf out of FDA's book, when the Agency decided (admittedly initially against its will) to discuss specific issues concerning aseptic processing with the industry and others in 2002/2003 under the *aegis* of PQRI. The end product of that process was real success in understanding, appreciating and implementing scientific solutions for critical issues such as process simulation output, and the inclusion of this particular rationale into Annex 1 is a *de facto* product of industry liaison. Just think of the potential benefits of the European regulators if they could do the same.

About the Author

Martyn Becker is now managing Director of Martyn Becker Associates, Ltd., a consulting company in the UK. He previously worked for Merck, SmithKline Beecham in the UK and as an inspector for the MHRA, where he attained the title of Senior Inspector (steriles and biologicals) and then ultimately as Southern Regional Manager. He has served on a number of regulatory liaison committees, including the PQRI Aseptic Working Group with successfully provided recommendations to FDA for inclusion into the 2004 FDA aseptic processing guidance. More recently he has formed part of an EFPIA expert working party that has input to the EMEA on the recent updating of EU GMP Annex 1 on sterile medicinal products.