The Challenges of Annex 1

A short overview on recent discussions around the implementation and interpretation of the revised Annex 1 to EU GMP-Guide

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The revised Annex 1 "Manufacture of sterile medicinal products" became effective on 1st March, 2009. The most significant revisions relate to

- cleanroom classification and monitoring,
- vial capping,
- media fills, and
- bioburden monitoring

Background

The publication of the revised Annex 1 in February 2008 was the result of a long and sometimes difficult process with the goal of both reflecting current science and technology as well as realizing a better harmonization between ISO standards, European and US Regulations.

A first draft with proposed updates was published on the EU website in late 2005 inviting industry comments. Discussions on this draft were ongoing through 2006 and led to the publication of a final draft in the first part of 2007, which was unfortunately not readily accepted by all EU-member states. So it took another year of discussions until the revision was ready for publication.

Besides EMEA, the stakeholders of all these discussions were an expert working group of the EFPIA, the European Committee for Standardization (SEN), members from the ISO cleanroom committee and the PDA.

The revisions in Annex 1 have added significance in that the EU GMPs are adopted by PIC/S and therefore will apply in member countries outside Europe.

Key Revisions to Annex 1

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<th>Classification and Monitoring</th>
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<td>differentiates the requirements for classification and monitoring (e.g., regarding sampling volume/frequency)</td>
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<td>clarifies the expectations for classifying under “at rest” and “in operation” conditions and for “in operation” routine monitoring</td>
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<td>aligns classification categories (Grades A-D) and sampling size/point/location requirements with ISO 14644</td>
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<td>stipulates for Grade A zones, particle monitoring for the full duration of critical processing, including equipment assembly (i.e. continuous monitoring); allows for sample frequency reduction in Grade B, and Grade C/D monitoring based on risk</td>
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<td>increases 5 micron particle limits to reflect method limitations and align better with ISO 14644</td>
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<td>states that 5 micron monitoring is an important diagnostic tool and that regular/consecutive counts should be investigated</td>
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<td>clarifies the expectations for automated particle monitoring in Grade A and B conditions, and calls for use of isokinetic probes</td>
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Vial Capping

- requires partially stoppered vials of freeze dried product to be maintained under Grade A conditions until stopper is fully inserted
- provides that vial capping can be applied in a Grade A/B aseptic area or alternatively outside as a clean process under a Grade A air supply
- calls for vial crimping equipment to be at a separate station due to particulate formation
- states that aseptically filled vial stoppers are not integral until cap is crimped
- clarifies that vials with missing/displaced stoppers should be rejected prior to capping, and urges using technology rather than human intervention
- espouses benefit of RABS and isolators in capping
Media Fills
- aligns the media fill requirements with FDA’s 2004 aseptic processing guidance
- clarifies that investigation of gross failures should extend to batches manufactured since last successful media fill

Bioburden Monitoring
- calls for per-batch pre-sterilization bioburden testing for terminal sterilization and sterile filtration in line with the 1996 EU mandate and inspection practice
- allows monitoring “at suitable intervals” where overkill sterilization is used and allows in-process bioburden testing for parametric release

Discussion topics
The implications of the revised Annex 1 have been a focal point at recent public conferences and workshops in Europe and the US. Among the issues that are surfacing is how much trust manufacturers are willing to place on their own science and risk assessments when they lead to different conclusions and approaches from the Annex 1 provisions and/or the other standards. Of concern is not only the strength of a firm’s process control understanding and application, but the ability of regulatory agency inspectors to make the same assessments and allow for QRM-based flexibility against the published benchmarks. Also at issue in the Annex 1 discussions is the role that regulatory guidance can and should play in helping improve industry practice and mitigate risk. Emerging into relief is the inherent tension between prescriptive rules and the science and risk-based thrust of the quality regulatory initiatives underway in the United States and Europe, and internationally through ICH, intended to provide a more continuous improvement/technology friendly compliance environment. The manufacturing difficulty and the stern consequences of failure increase this tension in the aseptic processing context. Besides these fundamental considerations, a lot of technical discussions came up.

Classification and Monitoring
The general industry consensus as voiced at the forums is that the revisions to Annex 1 for the most part did help clarify and rationalize the EMEA’s compliance expectations while leaving enough flexibility for the expectations to be met under varying manufacturing circumstances and technology applications. Appreciation was expressed at the forums for the clarification in the revised annex of the cleanroom qualification and monitoring requirements at rest and in operation and their differentiation. Also appreciated was the lining up of the particle limits and air sample size and location requirements for the EU Grade A-D zone system with the ISO classes, thereby eliminating the confusion inherent in the former version. However, the discussions also pointed to potential interpretation and implementation trouble spots, and raised concerns about the underlying foundation on which specific mandates were based. At issue is whether these prescriptions, while achievable, hold up against scientific and risk analysis and whether they are directing valuable control resources at the most effective targets. Points of discussion are especially
- the significance of the choice of 20 for the Grade A particle limit
- the necessity of 5 micron monitoring in addition to 0.5 micron monitoring
- the implications of continuous monitoring in Grade A zones, especially during equipment assembling
- the interpretation of the recommended limits for microbial monitoring and the meaning of “average value” in this context
- the setting of alert limits for microbial monitoring

Vial Capping
Generating the most concern during the Annex 1 discussions was the issue of vial capping and the annex statements on the specific conditions and vial handling constraints around stoppering and stopper oversealing. The capping debate brought into full relief the problems inherent to the interpretation and implementation of prescriptive regulatory guidance and the tension with a science and QRM approach that specific mandates create. Points of discussion are especially the rationale for the statement that the container closure system is not fully integral until the aluminum cap has been crimped into place the capping provisions.
Guidance versus Rule
The conversations at the forums about the specific provisions in Annex 1, and those related to capping in particular, flowed into a larger dialogue on quality regulatory guidance – how it should be developed and what it should and should not try to accomplish.

Paul Hargreaves, MHRA Principal Medicines Inspector and member of the EMEA working group drafting the Annex 1 revision, pointed out that the annex, like the rest of the EU GMPs, is not written as a prescriptive rule but as a guide. As such, it is important for companies to understand the principles it espouses and interpret and apply them as they fit best into their own quality systems and processes. In Annex 1, the underlying principle is minimizing the risk of microbial, particulate and endotoxin contamination.

While the EU-GMP-Guide in general states that what it says is the approved way of doing things, it also recognizes that alternative approaches are allowable if it can be demonstrated that they are at least equivalent to what is written in the guidance. These alternative approaches must be scientific, logical, justifiable, documented and supported by appropriate data and information.

Prescriptive Guidance versus Harmonization
Another topic for discussion was the discrepancy between prescriptive guidance and the pursuit of international harmonization. Detailed mandates often do not line up across regulatory agencies. Therefore guidelines intended to convey principles rather than “how to’s” are more compatible with the harmonization effort, as the ICH process has demonstrated.

Annex 1 is only one of a number of global aseptic processing requirements, including the US document and similar ones in Japan, Canada, Australia, and the WHO, which has its own GMP guide and Annex 1 equivalent. Harmonization is therefore something of an issue, and this is something that the international community is going to have to deal with in the years to come. The philosophy is the same – we are all looking at the health, safety and well being of the patient at the end of the day. How we do it, the detail of it, is often a little different.

From worst-case to QRM-based Guidance
A crucial aspect of the harmonization problem is how to move from a prescriptive, worst-case mindset, which Annex 1 and other regulatory standards reflect, to a more flexible, QRM / continuous improvement orientation through which harmonization can more easily be accomplished.

The regulatory emphasis in setting standards in the past has been more on preventing the bad industry practice that has come to regulator attention through inspections and product problems than fostering new, more advanced solutions. The ICH initiatives are helping drive toward this less prescriptive, more risk-based approach, and the GMPs are going in that direction where we have much more freedom.

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