

European Sterile Products Guidance Under Review

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Introduction

Sterile manufacturing is arguably the most difficult and important facet of the preparation of pharmaceutical medicines (whether these are manufactured on a large industrial scale by a multinational company or on a named patient basis within a hospital pharmacy). This is because the medicines, due to their route of administration, are required to be sterile and if they are not sterile then this could lead to patient harm or even death. With microbiological contamination, the main risk concerns are:

- Viable microorganisms.
- Particulate matter.
- Pyrogens (including bacterial endotoxin.)

In the context of these risks, sterility is achieved through protective controls and good practices during processing and by the presentation of the final dosage form. For this reason, the production of sterile products is subject to a strong regulatory oversight. The two leading agencies for this are the FDA and the European Union (through national regulatory agencies.)

Annex 1 to the European Union Good Manufacturing Practice (GMP) guidelines is now under formal revision, with a concept paper issued during February 2015 and with a view to implement the new document during 2016. Annex 1 is a key part of European GMP for it affects the production and filling of sterile products. The document is also of global importance as manufacturing centers importing into Europe need to comply with the guidance. In addition, previous versions of the Annex have proven to be influential on other international regulators.

EU GMP Annex 1

European GMP relates to European Commission Directive 2003/94/EC which describes principles and guidelines of Good Manufacturing Practice in respect of medicinal products for human use and investigational medicinal products for human use¹. EU GMP contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in European Commission Directives. European GMP is overseen by the European Medicines Agency (EMA) and enforced by national inspection agencies (for example, in the UK this is the Medicines and Healthcare Regulatory Agency).

Annex 1 of the guidance contains information relating to the product and filling of sterile products². By this, it includes reference to aseptically filled products, blow-fill-seal and terminally sterilized products. The full title of the Annex is "EU GMP Annex 1: Manufacture of Sterile Medicinal Products."

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The Annex covers such areas as:

- Bioburden testing
- Sterilizing grade filters
- Cleanroom design and certification
- Particles
- Viable environmental monitoring and recommended limits
- Staff and behaviors
- Gowning requirements
- Disinfection and sanitation
- Validation and qualification
- Media simulation trials
- Sterilization and biological indicators
- Quality control

The scope of the current Annex reads:

“The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.”

The Future Guidance for Sterile Products

The European Medicines Agency (EMA) has issued a concept paper in which it is recommended to revise the current annex 1 of the European GMP Guidelines, on the manufacture of sterile products³. A public consultation is now under way on this concept paper, with a deadline of 31 March 2015. The update is likely to be significant given that the last, relatively extensive revision of Annex 1 dates back to 2007.

As to what the new revision is likely to bring, the European working party scoping document provides some clues.

Broadening the Scope

Although Annex 1 refers primarily to sterile products, the revised version is likely to consider all manufacturing steps that contribute to the production of sterile products. This means widening what is covered beyond sterile products and including the conditions of the manufacture of some non-sterile finished products and the early stages in the manufacture of sterile products (given that step up until the sterilization step are essentially non-sterile and are undertaken within lower grade cleanrooms.) This could include bioburden determination; cleaning validation; equipment design and so on.

Quality Risk Management

The revised guideline is set to clarify to what extent the ICH (International Conference on Harmonization) quality risk management documents apply to sterile products manufacture and how the abstract concepts of risk and hazard can be incorporated into the process workflow. In particular, the guidance is likely to recommend that ICH documents Q9 (Quality Risk Management)⁴ and Q10 (Pharmaceutical Quality System)⁵ should be followed in the design and implementation of facilities, equipment and processes for the manufacture of sterile medicinal products.

ICH Q9 is a practicality based document and it contains risk assessment methodology. The core part of ICH Q9 is the presentation of risk assessment methods. Two important points to remember for any risk assessment approach are that, first, there is no such thing as zero risk and therefore a decision is required as to what is acceptable risk. Secondly, risk assessment is not an exact science - different people will have a different perspective on the same hazard.

In ICH Q9 three key risk definitions are outlined. These help to contextualize what is meant by ‘risks’⁶:

- Risk: The combination of the probability of occurrence of harm and the severity of that harm
- Harm: Damage to health, including the damage that can occur from loss of product quality or availability
- Hazard: The potential source of harm

There are various risk assessment methodologies outlined in ICH Q9 including the two that are arguably the most useful: Hazard Analysis and Critical Control Points (HACCP) and FMEA (Failure Modes and Effects Analysis).

ICH Q10 describes a detailed model for an effective pharmaceutical quality system. This includes:

- Pharmaceutical development
- Technology transfer
- Commercial manufacturing
- Product discontinuation

These aspects are designed to come together to establish, implement and maintain a quality system that ensures the delivery of pharmaceutical and healthcare products with the appropriate quality attributes to meet the needs of patients.

Water Systems

One of the key divides between the United States Pharmacopeia (USP) and the European Pharmacopeia (Ph. Eur.) has been with the methods used to produce Water-for-Injections (WFI). Under the USP, WFI can be produced

using either distillation or reverse osmosis. Currently, Ph. Eur. only permits distillation to be used. Distillation refers to a process whereby component substances from a liquid mixture are separated through the combination of selective evaporation and condensation. Reverse osmosis uses a semi-permeable membrane to remove larger particles from water through the application of an applied pressure.

The difference between the two compendia dates back to times when reverse osmosis methods were less efficient at bacterial endotoxin removal. In light of current technologies, Ph. Eur. is set to change and allow both distillation and reverse osmosis to be used (although there has yet to be any formal announcement from the body which oversees the European Pharmacopeia, the EDQM (European Directorate for the Quality of Medicines & HealthCare)). Tracking this, Annex 1 will also change to allow methods other than distillation for the production of water for injection.

Embracing New Technologies

The current Annex 1 makes reference to measures to terminally sterilize products and to aseptic filling. Both of these strands are described in terms of classic methods. With terminal sterilization a greater range of sterilization methods, in addition to moist and dry heat, are likely to be included such as hydrogen peroxide vapor; ethylene oxide and gamma radiation.

With aseptic filling, although isolators are mentioned the current emphasis is upon a filling machine within a cleanroom (a Grade A unidirectional airflow device, what is close to an ISO 14644: 1999 class 5 environment, located within an EU GMP Grade B cleanroom (ISO 14644:199 class 7 in operation.) The indication is that the wider use of isolators will be included.

Furthermore, other methods for environmental monitoring, such as spectrophotometric real-time particle counters could be included. Such counts can differentiate between inert and biologic particles within a given volume of air⁷. In relation to environmental controls and environmental monitoring, the proposal reads: “embrace the use of new technologies to prevent detrimental impact on product and also to encourage the introduction of new technologies that are not currently covered.”

Cleanroom Certification

With the global cleanroom standard ISO 14644 part 1 (1999) and part 2 (2000) under review, the implications of these changes are likely to impact on Annex 1, given that both parts of the standard are referenced. The current status of these standards is that they were presented as a DIS (draft international standard) and have recently been accepted by international voting. The revised cleanroom standards are expected to be in place during 2015.

Annex 1 will need to reflect the intended changes to ISO 14644. In particular, the revision to part 1 contains a more appropriate statistical basis for classifying cleanrooms and clean air devices, and recognizes the problems and issues of sampling air with low concentrations of larger particles present. There is specific guidance provided for dealing with particles greater than and equal to 5 microns in diameter in ISO 5 and cleaner. The 5 micron particle issue is one of the chief divides between the FDA 2004 guidance on aseptic filling⁸, with calls for monitoring particles of a size equal to or greater than 0.5 micron only, and Annex 1, which currently seeks particles of 0.5 (and greater) and 5.0 (and greater) to be measured for both cleanroom classification and in terms of continuous particle counting.

The revision to ISO 14644 part 2 now includes specific guidance on airborne particle monitoring as well as other specific cleanroom performance parameters. Aspects of this may also fall into the revised Annex 1.

Revision Timetable

In terms of driving the changes through, a drafting group will be established by GMP/GDP Inspectors Working Group and the PIC/S Committee. The co-ordination will be undertaken through the U.K. regulatory agency, the MHRA (Medicines and Healthcare products Regulatory Agency.) There will also be input from non-EU PIC/S participating authorities. PIC/S is an international convention of pharmaceutical regulators (the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme). This includes the FDA.

Furthermore, given that the last review of sterile products manufacture by FDA was in 2004, the content in the revised European document could prove to be influential.

Summary

The forthcoming changes to Annex 1 are likely to provide an important signal to the industry as to the expectations of regulators (both within Europe and worldwide.) The information provided within the scoping document signals a need to embrace new technologies, both designed to protect products from contamination and to monitor the environments within which such products are produced. Following the various initiatives in relation to quality risk management and Process Analytical Technology (PAT) at the start of the twenty-first century⁹, it will be interesting to see whether the new guidance takes these concepts forward further and what additional measures regulators expect in terms of enhancing contamination control measures.

References

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