Standards for Imaging Endpoints and Manufacturing of PET Radiopharmaceuticals

Industry Perspective on PET Manufacturing Comparison of EU and US Guidances and associated Regulations

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Discussion topics

Convergence on Longitudinal Quantitation

Imaging for patient care and drug R&D

Medical Imaging Drug Advisory Committee

Rigor and consistency in external advice

Guidance for global innovation

Harmonization of Guidances, interpretation

Background:

Industry and academia have been struggling over many years to determine what would be an acceptable standard of the “Quality” that should be applied to PET drug manufacture:

This has lead to different views between different organisations.

The extreme views

1) The PET community should follow, as close as possible, the rules and cGMPs applicable to the manufacturing of conventional pharmaceuticals. Where this is not possible, due to the intrinsic hazards and short shelf lives of PET products, methods that will give equal or greater levels of quality and patient safety should be used.

2) PET drugs production is not manufacture, but an extension of compounding. As such it should be performed under the direction and supervision of a nuclear pharmacist and regulated by State Hospital Pharmacy Boards.

Our view

In reality neither of these extreme views adequately describes the controls required for PET manufacturing.

Traditional pharmaceutical GMP's are not suitable for complex PET manufacture, and the pharmacy approach has resulted in wide ranging differences in the quality of facilities.

What is needed is detailed guidance to enable producers to understand FDA's requirements. This would establish a "bench mark" for existing producers, and provide design criteria for new facilities.

PET Drugs — Current Good Manufacturing Practice (CGMP) issued Dec 09 become effective Dec 11

The new PET CGMP document is welcomed as it provides guidance on the Quality Management systems that FDA expects for PET manufacturing.

However the document leaves room for interpretation of FDA's expectations on the quality of facility design.

Because of this room for interpretation, uncertainty in the PET community resulted as to what FDA investigators expectations will be when inspecting their facility.

Other regulators have been more proscriptive in their PET GMP requirements

Examples

The required background to the class 100 (ISO 5) critical aseptic zone

Specification of environmental conditions for terminal sterilization

Distinguishing two ways of aseptically filling product

Specifications for environmental and personnel monitoring

Queries on cGMP and NDAs

Documentation

What can be centralized, eg documentation of CMC

Multi-site production of new PET drug; stability

Question: What is FDA expectation on stability data to be included in NDA from each site?

Process verification requirements, USP v GMP

Question: USP 823 requires 3 batches for process verification. In the new 21 CFR part 212 process verification is not required for products that undergo full finished product testing. Could the agency please clarify?

Manufacturing vs Pharmacy Practice; closures

Question: What is FDA expectation on data in NDA on container closure, compatibility testing and stability testing from pharmacy practice?

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Thanks to FDA, RSNA, and SNM for the opportunity to contribute

GE imagination at work

Other countries/organisations have been more clear in their PET GMP requirements

Examples: The required background to the class 100 (ISO 5) critical aseptic zone in which the aseptic manipulations are performed. (e.g what background should a Laminar Air Flow workbench (LAFW) be sited in)

FDA Guidance: *Conditions in the room where aseptic manipulations are conducted should not present a challenge to the operating capability of the aseptic workstation*.

European Union: *LAFW should be class A (ISO 4.8) and sited in a Class B environment (ISO 7 in operation*).

Australia: *The use of a laminar flow hot cell that provides Grade A (ISO 4.8) conditions located in a Grade D (ISO 8) room for aseptic processing steps is acceptable as this is equivalent to the use of an isolator for aseptic processing that is located in a Grade D room.*

Other countries/organisations have been more clear in their PET GMP requirements

(1) Terminal sterilization: environmental conditions

FDA Guidance: The sterilization technique is mentioned, but no guidance is given to the required environment to fill the vials to be autoclaved.

EU Guidance: PET GMP requirement refers back to the conventional pharmaceutical GMP requirements in annex 1 of the GMP guide. Here the detailed environmental requirements are stipulated.

Other countries/organisations have been more clear in their PET GMP requirements (2) Aseptic filling

Two ways of aseptically filling product:

•Open, where the product, or part of the dispensing apparatus that contacts the product, is exposed to the external environment

•Closed where the dispensing operation is performed using a sterile fluid path with a sterilising filter, where post filtration the product is never exposed to the external environment.

FDA Guidance: No differentiation is made between the two ways.

EU guidance: Distinction between the two methods, and guidance given on what controlled environments are suitable.

Other countries/organisations have been more clear in their PET GMP requirements

Environmental and Personnel Monitoring

FDA guidance:

Environmental monitoring is crucial to maintaining aseptic conditions. We recommend that microbiological testing of aseptic workstations be performed during sterility testing and critical aseptic manipulation. Methods can include using swabs or contact plates for surfaces and settling plates or dynamic air samplers for air quality.

EU guidance: Also requires particle counting during aseptic manipulations.

Question: FDA`s PET GMP`s do not mention particle counting during the aseptic process. **What are FDA's expectations?**