THE IRRADIATION PANEL

To: European Medicines Agency (EMA)

From: The Irradiation Panel Officers

Re: EU GMP Annex 12 update required

This note from The Irradiation Panel Officers is intended to underline the need for EMA to update Annex 12 'Use of ionising radiation in the manufacture of medicinal products'. This Annex has not been revised for many years and therefore it does not reflect the standards, practices and capabilities presently associated with ionising radiation technologies. The use of X-ray technology, in addition to gamma and electron beam technologies, as a process used for (bio)pharmaceutical sterilization must be recognised.

Qualifying X-rays as an alternative to gamma for sterilization of health care systems becomes imminently needed, and clear alignment is required between suppliers, (bio)pharmaceutical manufacturers and regulators on transition and business implementation expectations.

The Irradiation Panel is a body of experts with a membership covering a broad cross section of the radiation processing community with a key part of its mission to partner with regulatory authorities on standardising best practise and reflecting the European view in development of regulations, standards, and guidance.

Industrial radiation processing involves exposing a product to ionizing radiation of two types: photons and electron beams. Photons are emitted by radioactive sources like Cobalt 60 gamma or are generated by conversion of accelerated electrons into bremsstrahlung X-rays. These technologies are used in many industrial sectors such as medical device, pharmaceutical, packaging, automotive and cable industries.

While gamma and electron beam facilities have been in use throughout the world for several decades, X-ray facilities have been, and continue to be, subjected to rapid growth due to shortages in gamma irradiation capacity. X-rays advantageously complement the irradiation capacities worldwide due to similar penetration characteristics when compared to gamma rays.

X-ray irradiation is not a novel modality of ionizing radiation. Switching from radioactive photon sources to machine sources for industrial applications was possible when accelerators became powerful enough. A first facility fully dedicated to X-rays was installed in Europe followed by “Duo-installations” (Accelerator can produce both, electrons, and X-rays). Valuable experience was gathered mainly for the sterilization of medical devices and pharmaceutical products. In 2025, more than twenty X-ray facilities are expected to be in operation around the globe, accelerating the need for product qualification in this modality and recognition within Annex 12.

The same switch is also observed for the treatment of blood products for which the radioactive sources must be replaced by low energy X ray machines in Europe. This move is ongoing still.

As a matter of fact, all the requirements covered by Annex 12 for gamma and electron beam irradiation are fully applicable to X-ray. The Panel has drafted guidance on an approach to transfer between radiation technologies described by ISO 11137 – Sterilization of Healthcare Products – Radiation and can be found here.

Additionally, requirements of the current national and international standards (ISO 11137 series) that apply to performance qualification dose mapping, process control and dosimetry are not reflected in the current content of Annex 12. There is no reference to the requirements to establish the required (sterilization) dose, of the procedures necessary to verify that the specified dose remains efficacious, or of the need to verify the compatibility of the materials employed in association with the material being irradiated. The current content of Annex 12 reflects attitudes and procedures that were employed in irradiation processes for pharmaceuticals and medical devices in the 1980s and 90s, it is in urgent need of revision to make it fit for purpose.

The Irradiation Panel volunteers to contribute to updating Annex 12 in the light of this note and in the spirit of producing a document which is in line with international standards and guidance on radiation sterilization.