New Applications For Accelerators In Pharmaceutical Processes

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Abstract. In-line sterilization tunnels using electron beam have become a reality since the development of low energy and medium energy accelerators small enough to fit into self-shielded units which can be integrated into production lines. These systems have many advantages for the health care industry since they provide fast continuous room temperature sterilization which is simple to validate and traceable. Economies are apparent in terms of time, logistics, fixed assets costs, labour costs etc. Environmental impact is considered low. Medium energy systems for core sterilization of medical devices, syringes or vials have already been installed. The low energy surface sterilization systems which have been installed on over 20 pre-filled syringe lines have recently benefited from technology improvements which increase efficiency. The presentation discusses electron beam sterilization technology and its practical aspects for pharmaceutical manufacturers, i.e. dosimetry, validation, interfaces, monitoring and recording.

1. Introduction

By the 2000s the technology of sterilization by electron beam was already well established in the healthcare industry. Since the 1960s service centers and in-house sterilization plants containing high energy electron beam accelerators had been used to treat large volumes of products, mainly medical devices. The advantages of electron beam sterilization were well known: this fast, continuous, room temperature treatment leaves no residues and is straightforward to validate. The U.S. Food and Drug Administration has approved the use of this sterilization method. ISO standard 11137 [1] provides instructions for guaranteeing sterility without having to undertake Biological Indicator tests; the standard states that if the dose is achieved, sterility is achieved. Hence the dose received by the product is all that needs to be measured: “Dose is Dose”.

Since electron beams produce X-rays as a by-product, high energy accelerators in service centers or in in-house production facilities are installed in bunkers with 3 metre thick concrete walls to protect operators. Lower energy beams can be housed inside smaller, lighter protective shields, designed to ensure that irradiation levels around these sterilizers are well within legal limits for public areas. With the advent of smaller sized medium and low energy accelerators, in-line electron beam sterilization tunnels became a reality.

In the late 1990s an in-line electron beam sterilizer containing three low energy accelerators was designed. By 2009 around 25 units of this type had been installed or built. A medium energy in-line sterilizer has been designed and installed for complete sterilization of prefilled syringes or vials, terminal sterilization of medical devices or sterilization of components entering a clean area. These self-shielded electron beam tunnels are integrated with the pharmaceutical processes, both upstream and downstream.

The equipment, a combination of electrical, electronic and mechanical systems, is reliable and, with regular maintenance programs, down-time is minimal. The technology does not require use of consumable products such as chemicals and water. Operating costs are low and treatment is fast (seconds), making this an economic alternative to other sterilization methods.

2. Low Energy In-Line Tunnels

SterStar™ in-line transfer systems using electron beam accelerators were first installed in 2002 by Getinge Linac Technologies S.A.S. on two European sites, for sterilization of items entering a production line under isolator [2, 3] These self-shielded systems contain three low energy KeVAC™ (200 keV) beams in a triangular configuration (Figure 1) creating an electron beam curtain through which the product is conveyed, ensuring that the correct dose of irradiation reaches all areas of the product surface including hidden areas. In this case the product - plastic tubs containing pre-sterilized syringes – requires surface sterilization only. Table 1 summarizes the characteristics of the KeVAC accelerator.

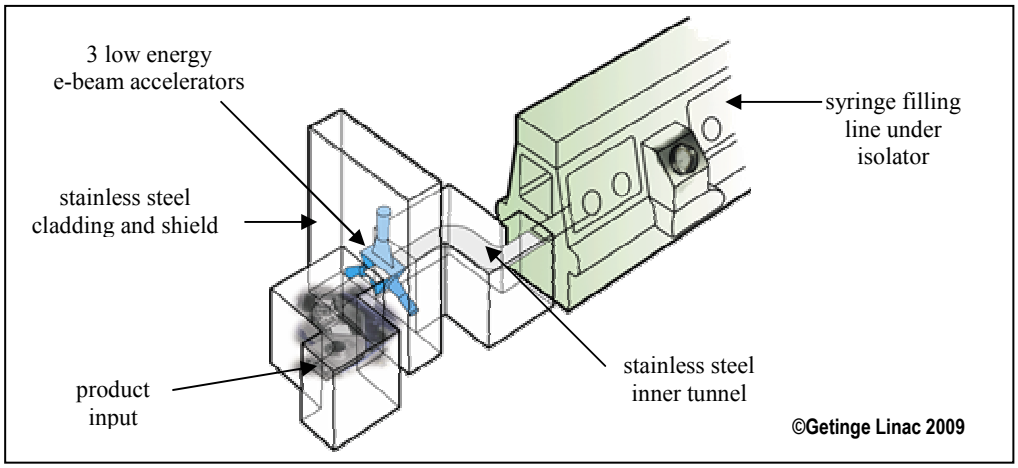

FIG. 1. SterStar™ Low Energy In-Line Tunnel located upstream of Filling Line under Isolator

TABLE 1: KEVAC ACCELERATOR CHARACTERISTICS

Beam Energy	Variable between 10 and 200 kV
Beam Power	800 W
Average Beam Current	From 0 to 5 mA
Scanning Width	From 7 cm to 20 cm (according to product size)
Conveyor Speed	According to product throughput
HV Generator	Continuous Voltage

These low-energy systems were particularly innovative since they could be installed directly in a production area thanks to their compact footprint. A typical shield is made of 1.5 cm thick lead alloy. Sophisticated control systems enable them to be integrated into the production line which is located inside a clean room. A stainless steel outer casing complies with GMP[1] requirements. Comprehensive safety systems are incorporated to ensure operator security. These include (non-exhaustive list):

- automatic system shutdown in a range of situations from the opening of the shield to the blockage of the conveyor belt;
- irradiation detectors mounted on the machine and in the production area;
- ozone monitors.

[1] GMP refers to the Good Manufacturing Practice Regulations promulgated by the US Food and Drug Administration under the authority of the Federal Food, Drug, and Cosmetic Act.

The e-beam transfer system is entirely integrated in the production process – in this case, a high speed filling line – both upstream and downstream (Figure 2). Control system software is fully compliant with 21 CFR part 11[2].

FIG. 2. Low Energy E-Beam Tunnel in Production Suite, Filling Line under Isolator in background

A major difference between sterilization centers using high energy electron beams and the new in-line systems is cleanliness. Whereas the high energy beam sterilizes products inside carton boxes, which are later handled by factory operators and other equipment, the products treated inside the low energy systems have a low bio-burden[3] at the outset and are kept sterile once past the e-beam curtain. An inner stainless steel tunnel is built around the conveyor, inside the lead shield. It is fully cleanable and is flushed with H_20_2 when the filling isolator is sterilized. During operation, airflow emanating from the filling isolator protects the inner tunnel and ensures that the ozone gas produced by the electron beam is forced out through the exhaust duct above the accelerators (Figure 3).

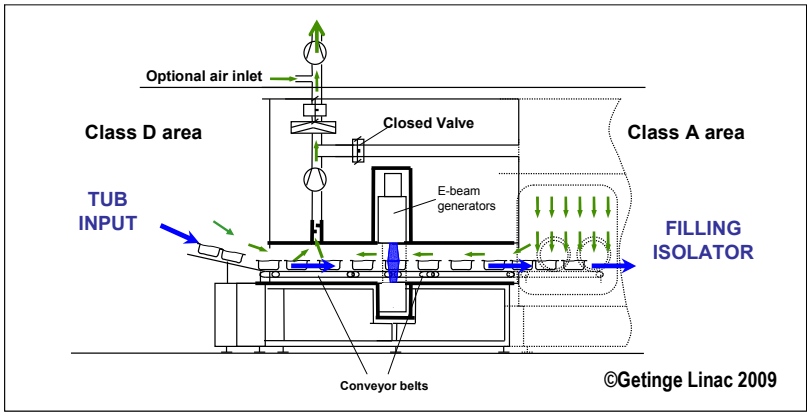

FIG. 3. SterStar2 diagram showing air flow

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[2] Title 21 CFR Part 11 of the Code of Federal Regulations deals with the FDA (U.S. Food and Drug Administration) guidelines on electronic records and electronic signatures in the United States. Part 11 defines the criteria under which electronic records and electronic signatures are considered to be trustworthy, reliable and equivalent to paper records.

[3] the number of microorganisms with which an object is contaminated.

In order to conform to new regulatory guidance for the manufacture of sterile medicinal products in Europe and the USA [4], a revised low energy system design incor-porates particle-reducing equipment [5]. This guarantees ISO 5 class [4] after the beam using recirculated uni-directional airflow which captures particles produced when the product is handled.

3. Medium Energy In-Line Tunnels

3.1. Medium Energy In-Line E-Beam Sterilizer For Complete Sterilization

Increasing use of the low energy systems in pharmaceutical production plants (19 had been installed by 2008) prompted the development of the SterBox™, an innovative self-shielded in-line sterilization tunnel using a medium energy accelerator (Figure 4) for complete sterilization of products. Beam power, beam energy, scanning area and conveyor speed (Table 2) are selected according to the product to be sterilized.

FIG. 4. Medium Energy Accelerator Inside Shield

TABLE 2: MEVAC ACCELERATOR CHARACTERISTICS

Beam Energy	3 to 5 MeV
Beam Power	3 to 15 kW
Average Beam Current	1 to 3 mA
Scanning Width	Bidirectional scan XY
Conveyor Speed	Up to 10 m / minute
HV Generator	Solid State Modulator

[4] An ISO class 5 cleanroom has at most 10^5 = 100,000 particles per m³.

Since more X-rays are produced as by-products of the medium energy beam, the lead shield is proportionally larger than that of the low energy system. The medium energy tunnel was designed as a "black box" containing the e-beam accelerators and associated electrical equipment (modulator, klystron, wave guide etc.), shield, product handling system, secondary cooling system and control system (Figure 5). The electrical cabinet and primary cooling system are installed nearby. An outer housing made of stainless steel panels fixed to an aluminium frame allows the units to be integrated in the production area.

FIG. 5. SterBox™ in Manufacturer's Workshop

The medium energy accelerator provides complete sterilization, both for sterile transfer of components entering a clean area and for terminal treatment of products after filling or at the end of a manufacturing process. The unit has a wide range of applications in the pharmaceutical and medical device industries [6].

3.2. Medium Energy E-Beam Sterilizer In-Line With Isolator

An in-line tunnel has been designed for sterilization of components being fed into an aseptic zone (Figure 6). Here, a stainless steel inner tunnel is incorporated inside the lead shield and two separate conveyors are installed to maintain aseptic conditions after the electron beam. A "jumper" beneath the beam separates the two zones.

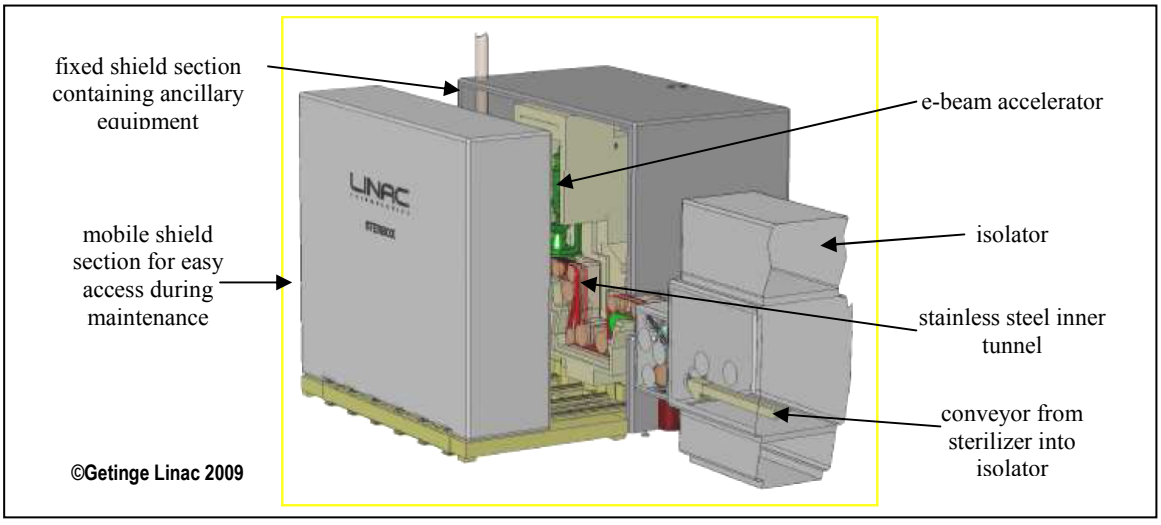

FIG. 6. SterBox™ linked to isolator

3.3. Medium Energy E-Beam Sterilizer With Rotating Conveyor System

A patented system (Figure 7) enables treatment of products larger than vials and syringes. This unit can be used for the sterilization of medical devices e.g. dialyser kits, infusion sets, etc. A patented shielded conveyor system ensures biological protection.

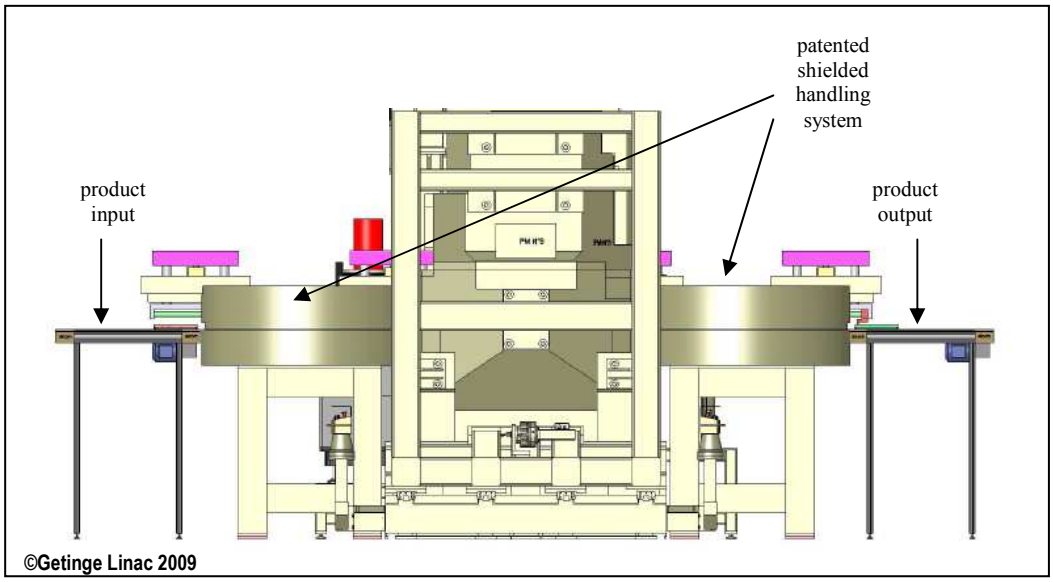

FIG. 7. SterBox™ with patented rotating shielded handling system

3.3. Medium Energy E-Beam Sterilizer With Two Accelerators

The "SterBox Twin" contains two medium energy MeVAC accelerators for treatment of high density products. Electron beam characteristics depend on the product to be sterilized. The speed of the treatment conveyor and the power of the accelerator are interlinked in order to ensure that a constant irradiation dose is present inside the product.

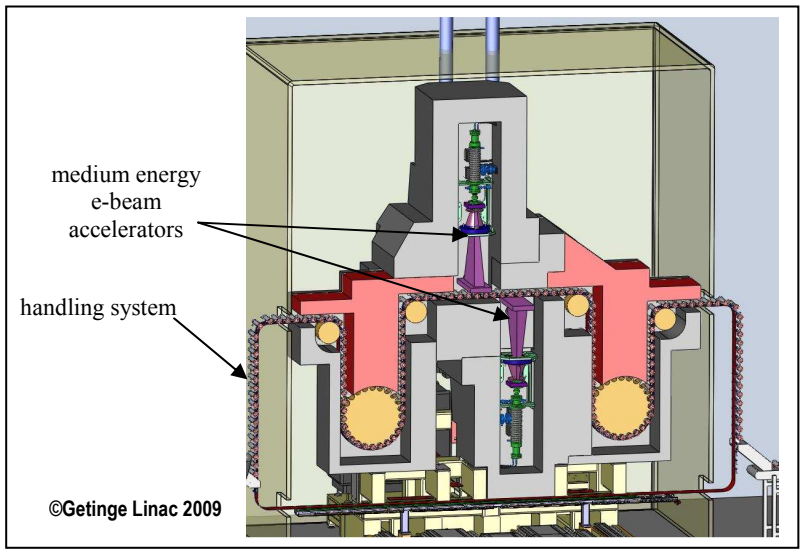

FIG. 8. SterBox™ Twin

4. Benefits For End-Users

The first two medium energy in-line tunnels have been installed in a production facility constructed specifically for this technology. Should the owner decide to switch production elsewhere, the tunnels can be dismantled, shipped and rebuilt at another site. This is one of the benefits for the end-user (summarized in Table 3 below) ensuring that in-line e-beam sterilization tunnels will be used for a wide variety of applications in the healthcare industry of the future.

TABLE 3: BENEFITS OF IN-LINE E-BEAMSTERILIZERS FOR THE PHARMACEUTICAL MANUFACTURER

In-line in-house machines for surface or complete sterilization	**Logistics and Capital Assets Economy**
Continuous treatment with recording of the GMP parameters	**Quality and Safety**
Flexibility of tuning for better dose distribution	**Quality and Economy**
Reliability and easy maintenance on site	**Quality and Economy**
Stand-alone equipment : easy to install, can be moved	**Economy**
Low operating costs	**Economy**
Packaging sterilization just prior to filling	**Quality and Economy**
Validation	**Simple to validate, traceable, recordable, meets standards**
Dosimetry / Sterilization	**Complete sterilization 7 log decrease[5] if required**
Environmental impact	**"Green" technology; no chemicals used, minimal exhaust products, comparatively low energy consumption**
Throughput and robustness	**Fast continuous sterilization High throughput in-line with process**
Interfacing with processes	**Fully integrated in the production process both upstream and downstream**
Pharmaceutical documentation	**Complete documentation provided according to GMP practices**

[5] a 10^{-7} decrease in the number of micro organisms present on a product after sterilization, compared with the initial bio-burden.

References

[1] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, ISO 11137-1, "Sterilisation of health care productions – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices" (2006)
[2] MORISSEAU, D., MALCOLM, F., "SterStar system : continuous sterile transfer by e-beam", Radiation Physics and Chemistry, 71, (2004) 555-558.
[3] CHMIELEWSKI, A. G., SADAT, T. and ZIMEK, Z. Electron accelerators for radiation sterilization. Trends in radiation sterilization of health care products. International Atomic Energy Agency, Vienna (2008) 40-41.
[4] SCHICHT, H., Regulatory Guidance for Manufacturing Sterile Pharmaceutical Products – Recent EC and FDA Developments, Bioprocessing and Biopartnering (Touchbriefings, London), (2006), 42-44.
[5] FONTCUBERTA, P., MALCOLM, F. and MORISSEAU, D. Further developments in low, medium and high energy accelerator facilities for sterilisation, material modification and research including complex turnkey installations. 15th International Meeting on Radiation Processing, London (September 2008).
[6] FONTCUBERTA P. In-line e-beam sterilization tunnel. PDA Pre-Filled Syringes Interest Group Meeting, Berlin (December 2008).