BGS
IDEEN PLUS ENERGIE

RADIATION STERILIZATION

PRODUCT SAFETY AS FINAL STEP IN PRODUCTION

WHO WE ARE

BETA-GAMMA-SERVICE GMBH & CO. KG, BGS in short, is among the pioneers of industrial application with accelerated electrons and gamma rays. Founded in Wiehl near Cologne in 1981 and to this day an independent and privately run company, we have shaped and co-developed groundbreaking methods in radiation sterilization and crosslinking. Through constant growth and our dynamic willingness to invest, BGS has developed into Germany's largest provider of irradiation services. At our three locations – Bruchsal near Karlsruhe, Saal an der Donau and the headquarters in Wiehl – we now have more than 200 employees and operate two gamma plants and eight electron accelerators.

In the field of sterilization, we already support our customers in the development stage.

In numerous industries and industrial sectors, irradiation serves as a final step in the process for placing the products on the market or generates new applications or creates cost-saving potentials in the manufacturing as a processing step. Thus, as a specialized service provider for radiation sterilization of sensitive goods such as medical devices as well as an expert for radiation crosslinking of plastics, we play a decisive role in our customers' value added chain.

Our services go far beyond the mere irradiation of products: In the field of sterilization, we already support our customers in the development stage by advising them on the selection of suitable materials for products and packaging, and the specification of optimal packing schemes for the irradiation. This includes, of course, the qualification, validation and related documentation of the sterilization process. In this way, BGS has been the reliable partner for many years now, when it comes to highly effective irradiation and experience in the special treatment of products that require sterility.

CONTENTS

WORKING TOGETHER AS PARTNERS

THE APPLICATION OF IONISING BETA AND GAMMA RAYS destroys pathogenic germs, moulds and spores fast, reliably and in an environmentally friendly manner. Radiation sterilization technologies are applied to products used in medical technology and biotechnology, pharmacy and research as well as food packaging, raw materials for the cosmetics industry, and a wide range of imported consumer goods such as toys or textiles. Through the physically acting radiation sterilization which takes place without residue and the use of chemicals, products are made safe for use - and are ready for immediate use after the treatment.

With this brochure, we, as the leading irradiation service provider in Germany, would like to contribute to answering central questions on the complex irradiation process and to impart knowledge about the requirements of radiation sterilization, such as validation, process integration or regulatory requirements. Just like other sterilization methods, radiation sterilization is subject to extensive legal and normative requirements that involve a high degree of initial effort for both the manufacturer and radiation service provider. It is therefore worthwhile for both sides to set up their cooperation for the long term - not only, but increasingly also with a view to the availability of sterilization and plant capacities throughout the entire market.

STERILIZATION WITH RAYS THE PHYSICS

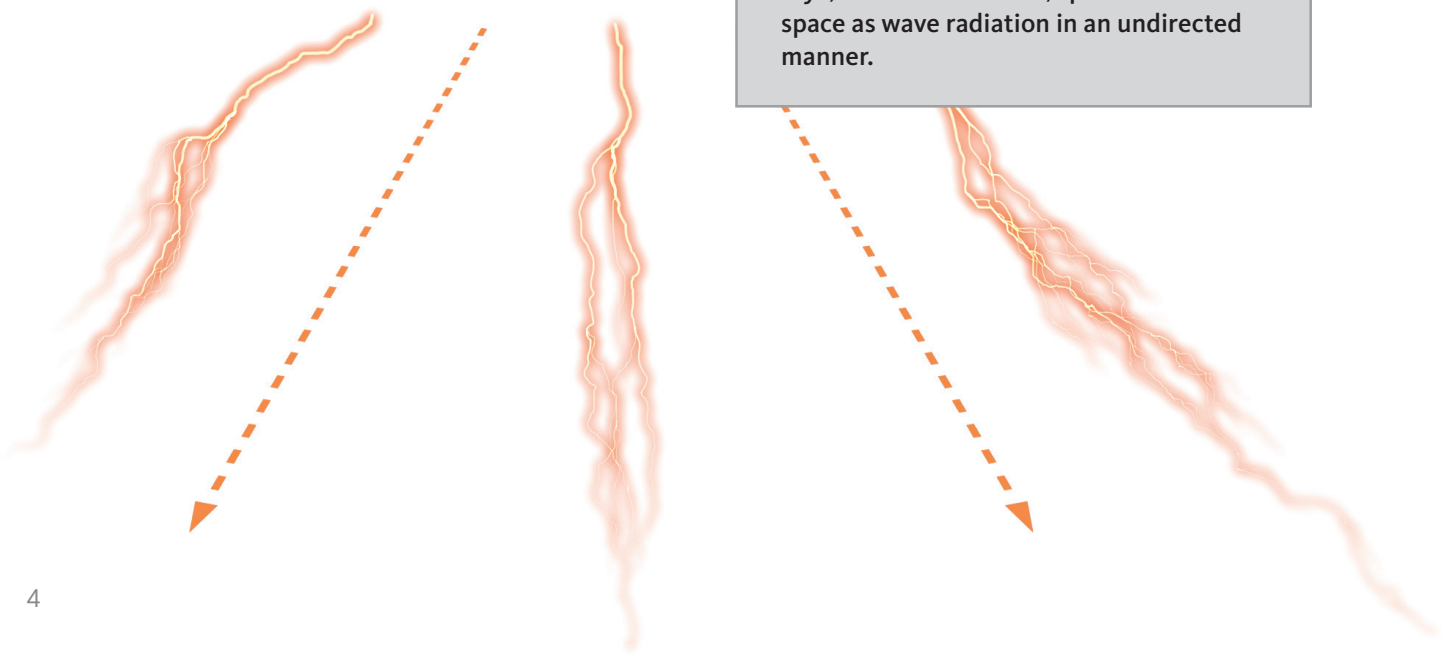
High-energy radiation is a form of energy that triggers chemical reactions. Contamination with microorganisms is thus reduced to a safe level for a wide range of products. Important to know: Due to physical limitations, the radiation used by BGS does not generate radioactivity. The treated products are also free from any residues and ready for immediate use.

For both radiation sterilization and radiation crosslinking, we use two types of radiation at BGS: electron beams and gamma rays. Electron radiation is a particle radiation where accelerated electrons act on atoms - on the product to be irradiated. Through the interaction of electrons with matter, electron radiation has a lower penetration depth compared to gamma radiation. As electromagnetic radiation, gamma rays have a much higher penetration capability.

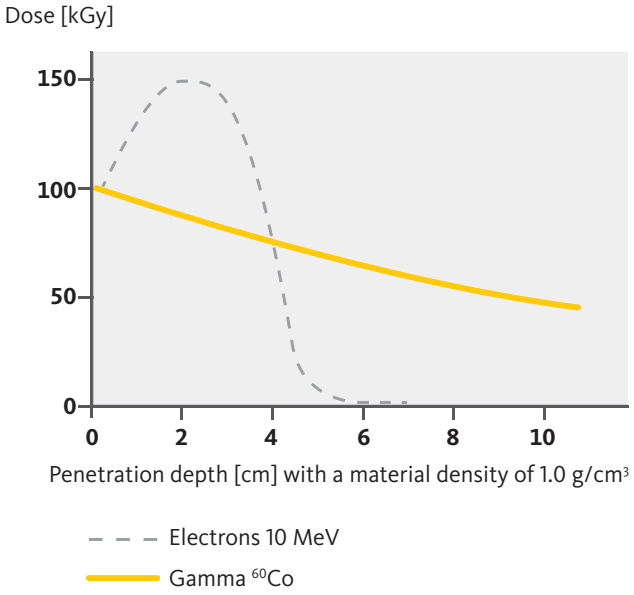
In plants with electron accelerators, high dose rates are used with a limited penetration depth, whereas gamma plants have high penetration capability and lower dose rates. This means that in electron accelerators, the required dose is applied to the product to be irradiated within seconds, for which hours are needed in the gamma plant. In gamma plants, however, greater volumes can be irradiated at the same time. Both types of radiation are suitable for sterilization and decontamination. The DNA of microorganisms is also reliably destroyed.

For physical reasons, it is impossible to generate any radioactivity with the alternative radiation sources used by BGS – electron beams up to a maximum energy of 10 MeV or gamma rays starting from the cobalt isotope ^{60}Co.

ELECTRON RADIATION is a particle radiation – indicated by arrows in the picture. It can be precisely directed in electric or magnetic fields. Electromagnetic gamma rays, on the other hand, spread out in space as wave radiation in an undirected manner.



PENETRATION CAPABILITY



X-RAYS

Besides electron beams and gamma rays, sterilization can also be carried out with X-rays. X-ray sterilization is suited for large quantities and products with high density. This method of sterilization is considered a new technology that is still in the development stages. Currently, we do not offer X-ray treatments at BGS.

Dose as an important parameter

In irradiation technology – as in all technical applications – there are specific parameters which enable irradiation to be measured, documented and reproduced. In both the sterilization and radiation crosslinking of plastics, it is primarily the radiation dose that specifies the desired result. Therefore, in radiation sterilization, the radiation dose determines the achievable degree of sterility (SAL = Sterility Assurance Level).

In terms of physics, the dose is defined as the radiation energy absorbed per mass. In the SI System, the unit Gray [Gy] is used today, named after the British physicist and radiobiologist, Louis Harald Gray (1905-1965). Formerly, the unit Rad (radiation absorbed dose) was used. The unit symbol is rd, but rad is almost always used.
1 Gy = 1 J/kg = 100 rad
10 kGy = 1 Mrad

The radiation energy absorbed by a product per unit of time, related to mass, is the dose rate. Its level plays an important role.
1 Gy/s = 1 W/kg = 0.36 Mrad/h

The penetration depth [s] of high-energy electrons and gamma rays depends on their energy (E) and the density (ρ) of the products to be irradiated.
The unit for measuring energy is joule [J], formerly electron volt [eV]. Electron volts are still frequently used today, as they provide figures that are easy to handle.
1 MeV (Mega electron volt) = 1.6 x 10^{-13} J = 0.16 pJ (picojoule)

The maximum penetration depth for irradiation from one side with electrons of energy E [MeV] into homogeneous material with density ρ [g/cm³] can be determined with the following formula:
s [mm] = (5.1 x E - 2.6) / ρ

The performance of a radioactive radiation source is characterised by its activity. In former times, the unit Curie [Ci] was used, named after Marie and Pierre Curie, who together with Antoine Henri Becquerel, were awarded the Nobel Prize in 1903 for the discovery of radioactivity. Nowadays, the SI unit becquerel [Bq] applies.

The becquerel specifies the number of atoms expected to decay per second according to the statistics of radioactive decay.
1 Bq = 1/s
1 Ci = 3.7 x 10^{10} Bq = 37 GBq

STERILIZATION WITH RAYS THE TECHNOLOGY

Gamma rays have a high penetration depth and a low dose rate. This enables the radiation penetration of entire pallets, which, however, may take several hours. Electron beams on the other hand, provide a high dose rate with a limited penetration depth. The irradiation of products packed in single cartons only takes a few seconds.

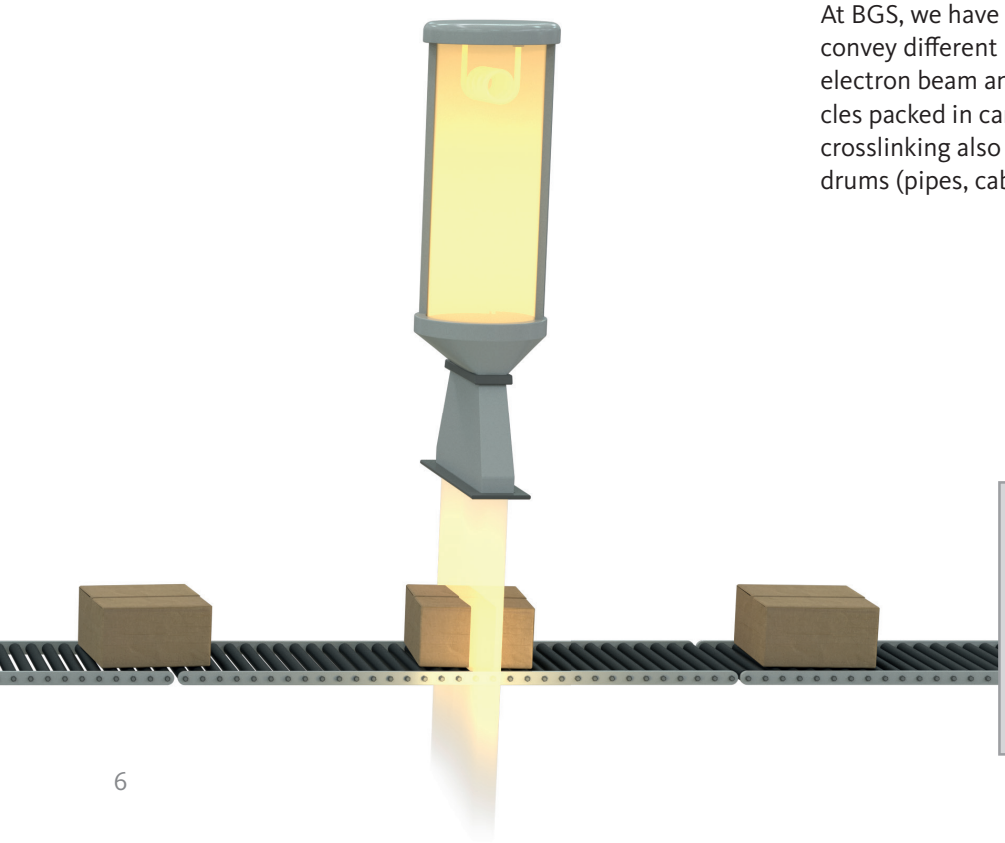
Electron accelerators

The principle of an electron accelerator can be compared to the Braun tube: A hot cathode emits electrons, which are accelerated in a strong electric field to near the speed of light. Their speed depends on the voltage applied between the hot cathode and the anode (earth potential).

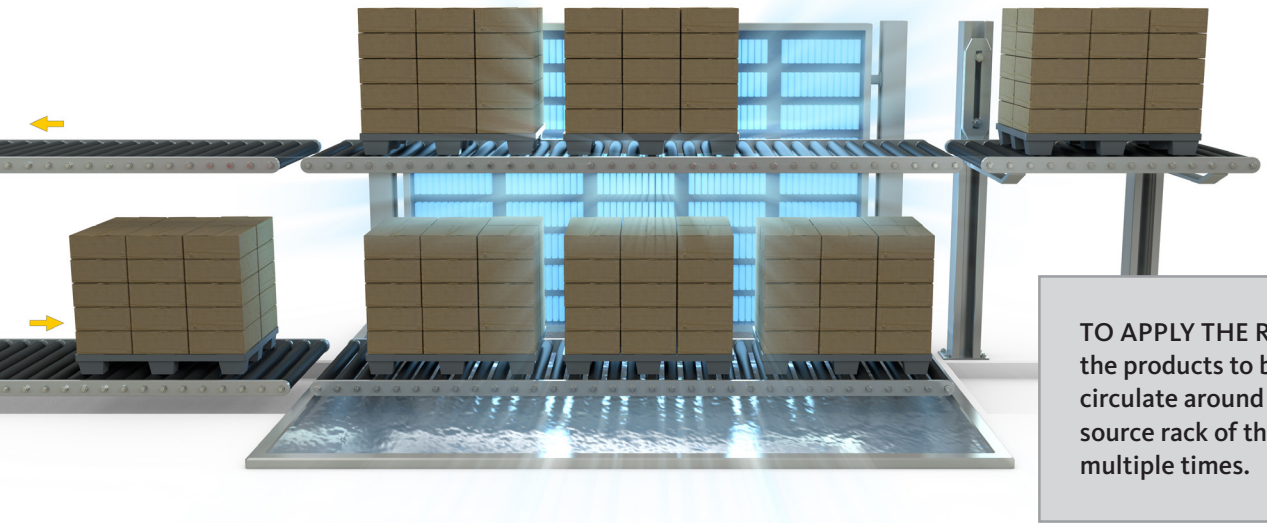
A high voltage is applied to the accelerator tube, which is under high vacuum. On leaving the cathode, the electrons are accelerated and focused. The beam is deflected in an alternating magnetic field, so that at the end of the scanner it reaches the product to be irradiated as a fan-shaped electron beam. The penetration depth of high-energy electrons depends on their energy, and thus on the acceleration voltage.

To avoid voltage flashovers, the electron accelerator is housed in a pressure tank with insulating gas. To shield the radiation, concrete walls surround the entire plant including the scanner with electron exit window. This ensures that the electron beam and the resulting X-ray brake radiation are absorbed and that persons working on the system are not endangered. When the beam current is switched off, the irradiation areas can be entered without danger.

At BGS, we have developed numerous devices to convey different products under the fan-shaped electron beam and ensure uniform irradiation: articles packed in cardboard packages, for irradiation crosslinking also elongated materials wound on drums (pipes, cables, tubes) or bulk goods.



AN ELECTRON ACCELERATOR generates electron beams that can be arranged in alternating magnetic fields. A fan-shaped beam finally meets the product to be irradiated.



TO APPLY THE REQUIRED DOSE, the products to be irradiated circulate around the Cobalt-60 source rack of the gamma plant multiple times.

Gamma plant

In industrial gamma irradiation plants, gamma plants in short, the radionuclide Cobalt-60 (^{60}Co) is normally used as a radiation source. For this purpose, stainless steel capsules, which safely enclose the ^{60}Co isotope, are integrated in a so-called source rack. This radiation source emits gamma rays with an average energy of about 1.3 MeV and a high penetration depth.

The dose absorbed during irradiation varies depending on the product and is controlled in each case by the dwell time in the radiation field. To apply the required total radiation dose, the products to be irradiated generally circulate around the source rack multiple times. Medical devices usually require a residence time of several hours.

At BGS, industry and/or Euro pallets are used as an irradiation unit. Several pallets can always be in the radiation field of the gamma plants at the same time. The maximum dimensions and maximum weight of pallets are precisely defined and set out in our specification sheets.

The gamma rays are reliably shielded by massive concrete walls. It is completely safe to stay outside the irradiation area even when the plant is in operation. In contrast to electron accelerators, it is not possible to switch off the radiation source itself in gamma plants. However, the irradiation area can still be entered, e.g. for maintenance purposes. For this purpose, the radiation source is shielded: It is lowered into a water basin several meters deep. The water column, which is then above the ^{60}Co sources, acts as a reliable shielding medium.

Through the decay, the ^{60}Co isotope loses about one percent of its activity every month, so that used material is replaced at regular intervals. The used material can be reprocessed and reused for other applications. After 200 years, the material has generally turned into harmless ^{60}Ni and lost all activity.

It is completely safe to stay outside the irradiation area even when the plant is in operation.

RADIATION PROTECTION

Radiation is harmful for all living beings. Therefore, the top priority for us is to protect our employees by ensuring that they are not exposed to radiation at any time. We achieve this through multi-level safety systems, which reliably prevent access to irradiation plants. Regular training courses in the areas of occupational safety and radiation protection also ensure that our employees are qualified according to the current state of the art and can operate our plants safely.

STERILITY THROUGH IRRADIATION

In the manufacturing process of medical devices, pharmaceutical primary packaging materials or biotechnology products, a separate sterilization step is always necessary. Here, radiation sterilization stands out with the absence of residues and process speed.

A medical device is sterile if the statistical probability of finding a viable microorganism on or in the device is less than 1:1,000,000. This is referred to as a SAL (Sterility Assurance Level) of 10^{-6}, as defined by the DIN EN 556-1 standard. Nevertheless, it is not possible to manufacture a sterile product, even using the greatest hygienic care and controlled production processes in the clean room. In order to achieve a sterile state, products have to undergo a subsequent sterilization process after their production. Only then are implants or disposable products for the operating theatre such as catheters, cannulas, stents or wound coverings safe for use on humans.

One of the most important industrial sterilization procedures is sterilization with rays. Through irradiation, pathogenic germs on products are destroyed reliably, in an environmentally friendly manner and within a short time. In the process, the radiation damages the DNA of microorganisms so that they reliably lose their ability to reproduce, or they die. Sterilization is carried out particularly frequently using gamma rays and increasingly, electron beams. X-ray sterilization is in the early stages of development.

As a physically active process, sterilization with electron or gamma irradiation is residue-free, takes place without any mentionable increase in temperature, and thus enables, for example, the sterilization of products in their sealed final packaging. The sterilized products are also ready for immediate use after treatment. Since the entire device is irradiated, radiation sterilization is also recommendable in the case of complicated geometries, whereby irradiation with electrons has some limitations depending on the structure and density of the device. Sterilization using rays is generally not suited for devices containing microelectronic components, since it would destroy the electronics.

In addition to radiation sterilization, chemical sterilization with ethylene oxide gas (ETO) is also a reliable and conventional method when it comes to converting products into a sterile state. Both methods have their merits; in part they complement each other. In the ETO procedure, the products are exposed to a sterilizing gas, ethylene oxide, in a vacuum chamber. This method is suggested, for example, if the plastic parts of a product react to the radiation due to embrittlement or other impairments. However, there are waiting times after ETO sterilization, as the gas must be allowed to escape from the material.

ETO is not suitable for thermolabile materials or materials in powder form and airtight packaged products. In such cases, radiation sterilization is used, also when it comes to complicated geometries or large surfaces.

DECISION IN 6 STEPS

In order to be able to assess in advance whether a product is suitable for irradiation, BGS has developed a decision-making aid that comprises six evaluation steps.

MATERIAL RESISTANCE TOWARDS IRRADIATION OVERVIEW OF FREQUENTLY REQUESTED POLYMERS			
Group	Polymers	Resistance	Remarks
Thermo-plastics	Polystyrene (PS)	**	Very resistant; discolouration possible in transparent types; impact-proof types less resistant
	Acrylonitrile butadiene styrene (ABS)	**	Breaks down at about 100 kGy; avoid high doses in impact-resistant settings
	Polycarbonate (PC)	**	Discolouration possible; special types with reduced yellowing obtainable; discolouration may disappear after annealing
	Aromatic polyesters (PET/PETG/PBT)	**	Extremely stable, retains its very good transparency; be sure to pre-dry prior to processing!
	Polyethylene (LDPE/HDPE/LLDPE/MDPE)	**	Crosslinked to higher strengths, at the same time reduction of elongation at break; LDPE most resistant
	Polymethyl methacrylate (PMMA)	*	Discolouration at about 20-40 kGy
	Cycloolefin copolymer (COC)	*	Retains its good transparency and impact strength
	Polyvinylchloride (PVC)	*	Standard types not suitable, release of corroding gases; special types with higher radiation resistance obtainable, discolouration possible
	Polypropylene (PP) copolymer	*	More stable than PP homopolymers; specially stabilised qualities are recommended
	Polyacetal (POM)	O	Not recommended, extremely brittle
	Polytetrafluorethylene (PTFE)	O	Breaks down rapidly, creates corroding gases, not suited
Elastomers	Ethylene propylene diene rubber (EPDM)	**	Possibly crosslink products in addition
	Ethylene vinyl acetate (EVA)	**	Possibly crosslink products in addition
	Silicones	*	Increase in shore hardness possible
	Butyl and halobutyl rubbers	*	Breaks down, sterilization only possible in very low dose windows

** well-suited * suitable with limitations O not recommendable

Material behaviour

Electron beams and gamma rays reliably destroy microorganisms, but may also modify the material properties of the products as an undesirable side reaction. This depends on the radiation dose applied. If the products are made of plastics, possible changes in material properties should already be considered during product design. Some plastic materials can be irradiated without any problems, others less well and some are not even suitable for the process. The data in the table on this page reflect empirical values on the behaviour of frequently requested plastics. Individual material tests provide information about possible dose-dependent material changes - this allows the maximum accepted dose for the irradiation parameters to be determined.

In order to be able to assess in advance, whether a product is suitable for irradiation, we at BGS have developed a decision-making aid that comprises six evaluation steps. The starting point is the evaluation of product structure and functionality as well as a quantitative classification. Is it a single product or product family? A decisive evaluation criterion relates to the selection of materials. Is the product made of a single material or a combination of several materials? The mechanical properties of metal or ceramics, for example, are not affected by irradiation. If plastic materials are used, the evaluation must be made in accordance with the material table. Furthermore, it has to be checked in advance whether the product contains water and thus allows the growth of germs. In addition, logistical aspects such as the size of the product, its form of delivery or its storage conditions must be evaluated in order to finally draw conclusions on the type of radiation and dose range for radiation sterilization.

Choosing the right sterilization method is a decision that goes beyond the sterility of a product to be achieved. In addition to maintaining the functionality within the potential duration of use, strategic parameters that have to be considered already during the development of a medical device include, amongst other things, the availability of sterilization procedures on the market or the time until market entry. To ensure a smooth sterilization process later on, close cooperation between the manufacturer and the sterilization service provider is of great advantage already in the design phase and during product development.

VALIDATION OF RADIATION STERILIZATION

The way to a sterile product requires a legally prescribed validation and the radiation sterilization processes are regulated by the procedural standard DIN EN ISO 11137. The validation is divided into three stages as follows: the microbiological, dosimetric and application-related validation, which are interdependent.

Validation is a complex process in the course of which proof is furnished that the normative demands made on the manufacturing of a medical device are fulfilled. Generally, a validation process precedes each sterilization. It is required, if a product is launched on the market, a second plant or a second supplier is qualified while maintaining the chosen method of sterilization, as well as a change from an established method to another method of sterilization, for example from gamma to e-beam.

In order to ensure successful validation, it is essential for the manufacturer, in close cooperation with the sterilization service provider, to plan the validation itself, the personnel and financial resources related to it, and the time schedule. This applies to the validation of new devices as well as for changes in devices already on the market.

In view of the numerous normative standards that apply for placing sterile medical devices on the market, validation processes in medicine technology are very complex. However, thorough preparation as well as close contact and early involvement of the sterilization service provider, validations can be reliably implemented. Due to the overall high effort for both partners, manufacturers and service providers, the commitment to enter into a long-term relationship plays a decisive strategic role and is a guarantor for joint economic success.

The validation of radiation sterilization is regulated by the procedural standard DIN EN ISO 11137 and is divided into three parts:

- the microbiological,
- the dosimetric and
- the application-related validation.

Microbiological validation

In the microbiological validation, the radiation dose is determined which will transpose a non-sterile product into a sterile one. For this purpose, the initial microbiological condition (bioburden) is first determined on representative samples. The term bioburden refers to the number of germs present on the surface of a product prior to its sterilization. Testing for bioburden is regulated in DIN ISO 11737-1 and is binding for manufacturers of medical devices.

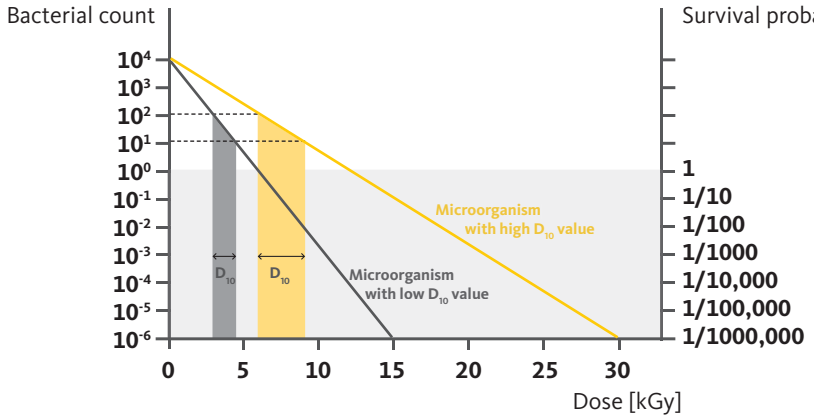
In the course of the second part of the microbiological validation, further sample items are subsequently irradiated with the so-called verification dose. This serves to furnish proof that all pieces can be transposed to a sterile condition using this dose.

To this end, different methods can be chosen which are described in the second part of the DIN EN ISO 11137 standard.

A distinction is made amongst the following procedures for microbiological validation:

- Method for procedure 1
- Method for procedure VD_{max}^{15} and VD_{max}^{25}
- Method for procedure 2
- Method for procedure VD_{max}^{SD}

EFFECTS OF IONISING RADIATION ON MICROORGANISMS



PARTNER FOR MICROBIOLOGICAL VALIDATION

We do not offer microbiological tests at BGS, but work together with accredited, external laboratories whose contacts we are happy to provide.

The method applied is dependent, for example, on

- the bacterial count and the initial microbiological situation,
- production conditions (degree of automation, production environment/clean room production/ manual work), materials selection (use of natural materials with a higher preliminary microbial load, such as cotton, or synthetic materials, e.g. plastics),
- batch size and production quantities (constant production, units)
- and also the costs.

Prior to revising the standard in 2006, methods 1 and 2 were the standard procedures. The procedures VD_{max}^{15} and VD_{max}^{25} have been added as new methods in the course of updating the standards. The latter are applied most frequently, since the first determination of a standard irradiation dose of 15 kGy (VD_{max}^{15}) or 25 kGy (VD_{max}^{25}) is possible at considerably reduced costs and testing efforts. Procedure 1 is the second most frequently used method. In comparison, procedure 2 is only very seldom chosen due to the high effort and expense and is not usable at BGS. With the procedure VD_{max}^{SD}, there are also currently alternative validation methods pursuant to ISO/DIS 13004:2021, which are attracting more and more attention.
The basic processes are comparable to the other VD_{max} methods and are not further described here.

Method for procedure 1

Determination of dose using the bioburden

In procedure 1, it is important to estimate how resistant the microbial population on the device is to irradiation. The tables set down in the DIN EN ISO 11137-2 standard specify this context. According to the average bioburden of a product, corresponding dose rates are stated in these tables, which guarantee a certain Sterility Assurance Level (SAL) in the case of a standard resistance distribution in the microbial population.

In the case of procedure 1, a SAL of 10^{-2} is chosen for the test with the verification dose. This means the validation can be recognized following irradiation of the devices with the relevant verification dose, if a maximum of two devices out of 100 show a positive result in the sterility test (i.e. are non-sterile). In this case, the germs found on the device are equally or less resistant to the irradiation treatment. If validation is successful, the required dose for routine radiation that guarantees a SAL of 10^{-6} can likewise be taken from the tables in the standard.

Method for VD_{max}^{25}

Confirmation of a selected sterilization dose

Similar to procedure 1, it is also important in the VD_{max}^{25} procedure to estimate whether the microbial population on the device is equally or less resistant to irradiation compared to the test. The tables of the DIN EN ISO 11137-2 standard are also used here for evaluating the dose. In the case of the VD_{max}^{25} method, a SAL of 10^{-1} is selected for the test with the verification dose. This means the validation can be recognized following irradiation of the devices with the relevant verification dose, if a maximum of one device out of ten shows a positive result in the sterility test (i.e. is non-sterile).

VALIDATION OF RADIATION STERILIZATION

In this case, the germs found on the device are equally or less resistant to the irradiation treatment. If validation is successful, a sterilization dose of 25 kGy is sufficient to guarantee a SAL of 10^{-6}. This method makes it possible to realize validation at considerably less cost since only ten devices have to be tested for sterility in the dose experiment rather than 100 individual irradiated product units. A further difference of the method VD_{max}^{25} to method 1 is the limitation of the average bioburden of 1,000 colony-forming units (CFU) per product unit.

The procedure using VD_{max}^{15} and VD_{max}^{SD} methods is comparable to the procedure VD_{max}^{25}. The main difference here is the limitation of the average bioburden per product unit.

Method for procedure 2

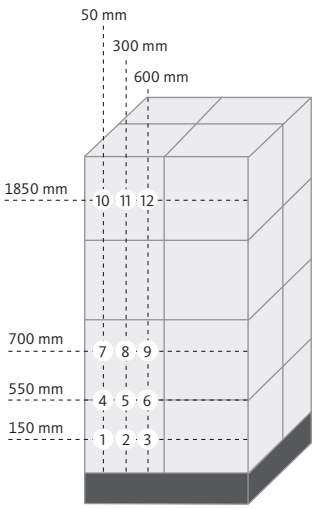
Determination of dose through extrapolation

Procedure 2 is seldom used due to its high complexity and the associated cost and effort of the validation. In this procedure, information about the resistance of the germs is gathered such as the germs that are actually on the products. In the process, a total of 280 product units are irradiated with gradually increased doses. Following successful irradiation, these 280 product units undergo a sterility test on an individual basis. For each dose level, the number of positive tests is subsequently determined. In the case of an increasing dose, the number of detected positive sterility tests decreases accordingly. This result reflects the resistance of the product-specific germs to irradiation.

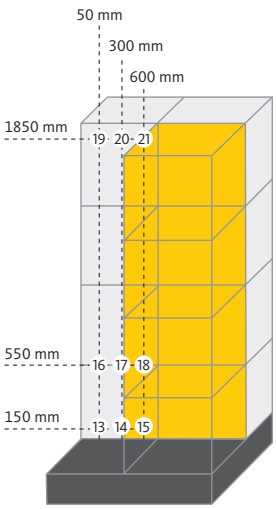
In the further course, a dose range is determined based on which a further 100 samples will be irradiated. This is the actual dose verification test. Following irradiation, these 100 samples also undergo a sterility test. The validation can be recognized following irradiation of the products with the relevant verification dose, if a maximum of two devices show a positive result in the sterility test (i.e. are non-sterile). This is equivalent to a SAL of 10^{-2}. The sterilization dose is then determined by means of an equation. In contrast to the procedures in method 1 and VD_{max}^{SD}, the bioburden is not determined outside of routine monitoring.

AS IN THE GAMMA PLANT, entire pallets are irradiated, the measuring levels on the pallets must be defined for the dosimetric validation in each case.

Dosimetric validation using gamma rays



Level 1: Front side of pallet



Level 2: Geometric median plane of pallet

Dosimetric validation (dose mapping)

The goal of the dosimetric validation, also referred to as dose mapping, is to describe the dose distribution in relation to a defined product arrangement in the packaging during irradiation. As results of this test, the positions of the minimal and maximal dose on the product are determined, and the resulting dose range for the routine monitoring positions is specified.

The following preliminary considerations are applied for the dosimetric validation and have to be defined:

- Number of dose mappings to be carried out
- Product (single article/processing class)
- Alignment of devices in the radiation field
- Evaluation of partial loads
- Packaging
- Arrangement of the products in the packaging

Results arising from determining the dose distribution are:

- Positions of maximum doses
- Positions of minimum doses
- Release limits for routine dose measurement to calculate the minimal and maximum dose
- In the case of multiple measurements, the uncertainty factors for the routine monitoring positions are taken into account

Application-related validation

In the case of application-related validations, the properties of the medical device and its primary packaging are evaluated following the completion of all manufacturing processes. Since not only the microorganisms are destroyed through radiation with electron beams and gamma rays, but the properties and functions of materials, packaging and products may change, these changes have to be examined. Changes in the device often correlate with the radiation dose. To be able to evaluate dose-induced changes, selected samples are irradiated with the maximum dose in very narrow limits and analysed subsequently. Depending on the device, different downstream tests are required.

In particular, polymer materials may change through irradiation. This is set against a background of chemical reactions triggered by radiation energy, such as crosslinking, chain scissions or degradation reactions in connection with atmospheric oxygen. The table on page 9 provides a first overview whether a material is generally suitable for radiation sterilization. In this context, only physical key figures were taken into account (e.g. heat deflection temperature, wear and friction, elastomeric properties, etc.). As a rule, metals, metal alloys and ceramics are stable towards irradiation.

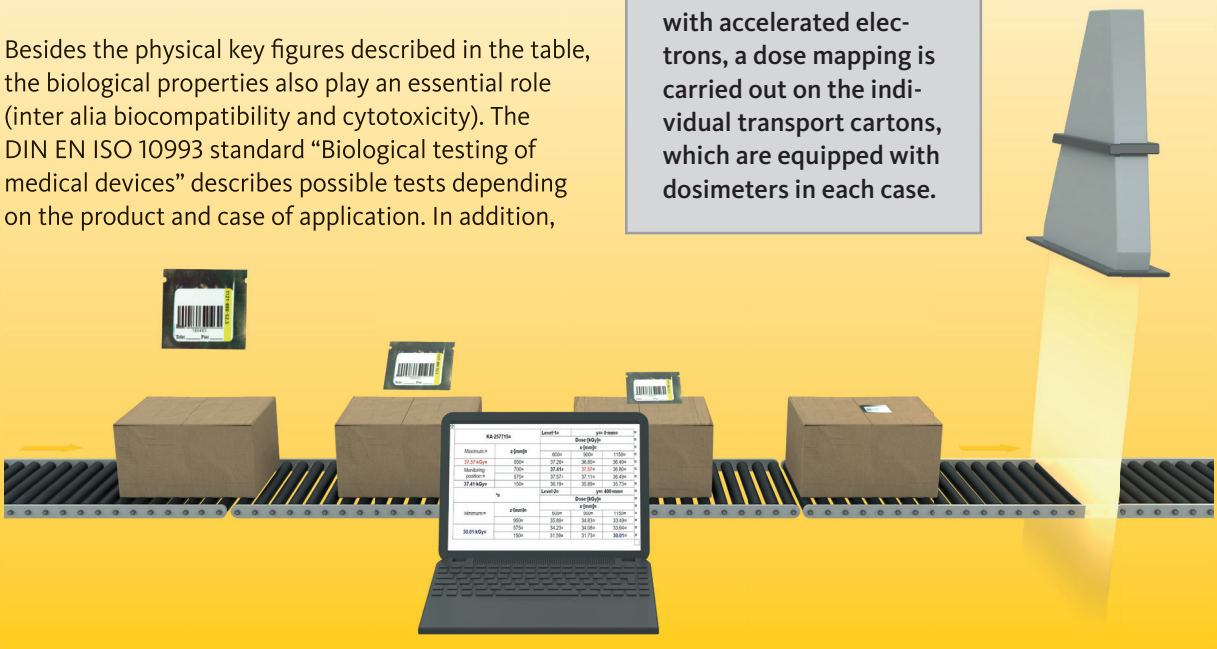
Besides the physical key figures described in the table, the biological properties also play an essential role (inter alia biocompatibility and cytotoxicity). The DIN EN ISO 10993 standard “Biological testing of medical devices” describes possible tests depending on the product and case of application. In addition, it has to be ensured that both the product as well as the primary packaging maintain the defined properties beyond the declared expiry date. To this end, laboratory tests are carried out to examine the integrity of the sealing seams and germ tightness of the packaging system. All the tests involved in this process are described via the packaging validation. Increasingly, the transport route of the medical devices is also being taken into account: A corresponding transport validation is being tested, for example, to study the influence logistic processes have on the product quality.

Revalidation

Those wishing to place sterile products on the market must furnish proof at regular intervals about the effectiveness of the sterilization method chosen. For this purpose, microbiological examinations are necessary at defined recurring time intervals. In addition to these examinations within the scope of the microbiological revalidation, all changes made to a medical device in the course of its lifetime are subject to an evaluation. In this context, it is particularly important whether the changes affect the quality of the devices.

If this is the case, suitable corrective action has to be taken. For the manufacturing step of sterilization, we recommend, together with the provider of the sterilization services, assessing how the changes affect the sterilization process in order to make necessary adjustments if required. Ideally, these changes should be announced sufficiently in advance, as it might be necessary to repeat part of the process validation or the entire validation under certain circumstances.

FOR THE IRRADIATION with accelerated electrons, a dose mapping is carried out on the individual transport cartons, which are equipped with dosimeters in each case.



STERILITY IN MEDICINE AND BIOTECHNOLOGY

THE MEDICAL TECHNOLOGY INDUSTRY IS REGARDED AS INNOVATIVE, future-oriented and fast-growing! Worldwide, conventional medical technology devices and basic equipment for medical care, for example, single-use products are more strongly in demand. In developing and emerging countries, this is mainly due to the demographic growth and rapidly increasing per capita income. In many industrialized countries, it is the demographic change that is leading to the strong increase in demand. With the rising demand, the need for sterilization capacities is also growing.

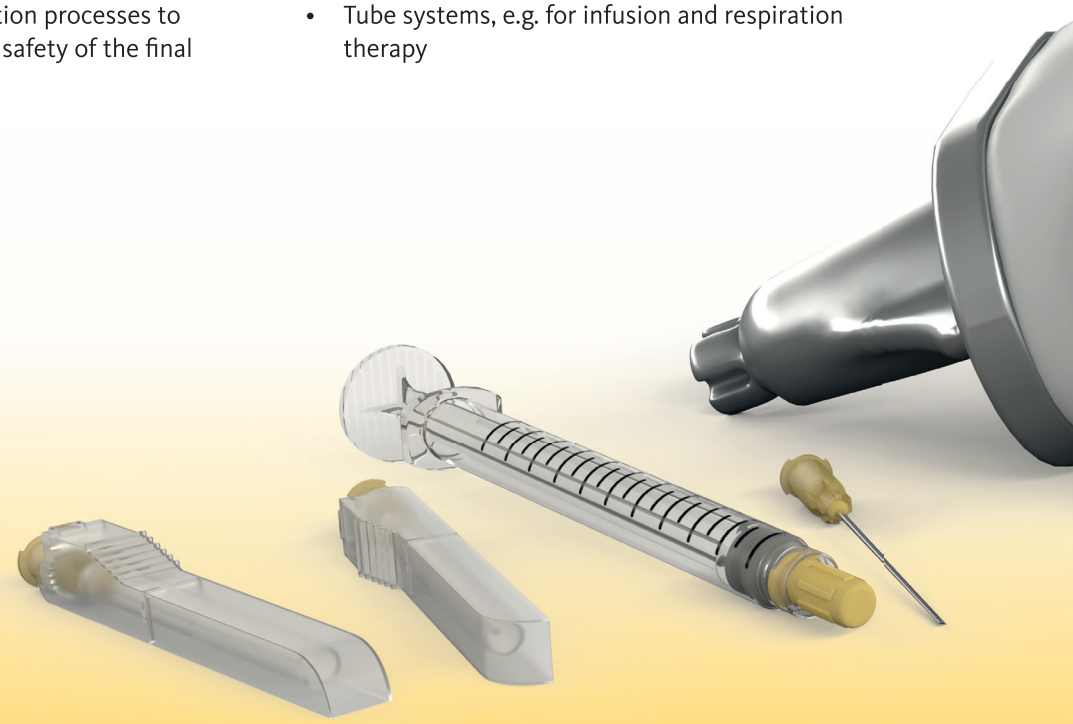
Medical items are just one of many product groups that we sterilize at BGS with electron beams or gamma rays. Equally important are pharmaceutical packaging, in vitro diagnostics and products from the biotechnology sector. Sterility is also indispensable in many industrial production processes to ensure consistent quality and safety of the final products.

Medical devices

In medicine, the use of sterile products and consumables is a matter of course. Nowadays, medical devices are multifunctional and are made from a large variety of materials. Despite their often complicated geometric structures, they must be sterile at every point. The sterility requirements are established by numerous standards, laws and regulations.

The devices sterilized by rays are medical single-use items before the first use. These include:

- Implants and prostheses
- Catheters, cannulas, dialyzers and blood tube systems
- Surgical drapes, instruments, gloves
- Dressings, stitching materials, wound management systems, hydrogels
- Tube systems, e.g. for infusion and respiration therapy



Industrial sterilization processes are subject to the stringent requirements of the German Medical Devices Law (MPG). BGS holds the necessary certifications and licenses and has many years of experience in dealing with international accreditation bodies such as the US Food and Drug Administration (FDA).

Biotechnology, pharmacy and research

Sterile working and input materials are also indispensable in biotechnology, pharmacy and research. In these industries, BGS sterilizes amongst others:

- Bioreactors
- Pharmaceutical primary packaging
- Handling and sampling working materials
- Container and dosage systems
- Packaging material
- Raw materials
- Laboratory supplies
- Culture media
- Plant substrates

In-vitro diagnostics and laboratory equipment

In-vitro diagnostics play a special role within medical devices. They are not used directly on the patient, but serve to analyse blood, tissue or urine, for example. Such test results must not be distorted by microorganisms that are contained in the vessels. Sterility is therefore essential for in-vitro diagnostics. Here, too, BGS provides the decisive contribution towards product safety. For example, with the radiation sterilization of

- Blood sampling systems
- Urine cups and stool sampling tubes
- Petri dishes, microtiter plates and PCR trays, reagent vessels
- Pipettes and pipette tips
- Disposable syringes

STERILITY MADE TO ORDER

WHILE MEDICAL PRODUCTS REQUIRE STERILITY, in many production processes of modern industry, sterility of raw materials and materials is essential to ensure reproducible results as well as quality and the safety of final products. This applies, for example, to foods, animal feed and personal care products or everyday items such as household goods or decorative articles. In particular, the manifold globalised trading processes bring about new challenges for consumer safety and hygiene. Specialised providers like BGS are able to treat goods in such a way that they are safe for consumers and the process of radiation treatment integrates optimally into the supply chain of customers.

Packaging

Each packaging material bears the risk of microbial burden on the product to be packed. Radiation sterilization prevents these microorganisms from passing to the fillers – for example, cosmetics or liquid foods. At BGS, even the inner surfaces of closed packages are reliably sterilized - the prerequisite for all products that have to be filled aseptically or into which no extraneous organisms may be brought in.

In many branches of the industry, sterility is a prerequisite for reproducible and high-quality production results. Radiation sterilization is used for packaging materials and processing aids made of metal or plastic for the cosmetics and pharmaceutical industry and for food packaging. In all such cases, we support the safety of the processing stages in these markets.

Raw materials

Without pigmentation raw materials, decorative cosmetics would be bleak. Therefore, it is all the more important that the colourants of plant origin used as an elementary component of cosmetics are safe and sterile. In their original state, plant pigments are often heavily burdened microbially.

As in the cosmetics industry, germ reduced and/or sterile raw materials are also basic materials for a large variety of products in many other sectors due to radiation treatment. Sterilization of natural raw materials is an important contribution to product safety. Positive additional effect of radiation sterilization: After treatment, the products have a significantly longer shelf life, preservatives become partly dispensable. Likewise, the health of people working in the further processing of the treated raw materials is no longer endangered by bioburdens.

These products are often only microbially safe after radiation treatment.

Consumer goods

Children should not be exposed to health risks - therefore toys must be safe. For decades now, we have been sterilizing toys on behalf of manufacturers and importers. Toys are often imported and contain "stowaways" in the form of most diverse microbes and pathogens. Our experts are familiar with the different requirements of the materials and specifically select the type, duration and intensity of irradiation.

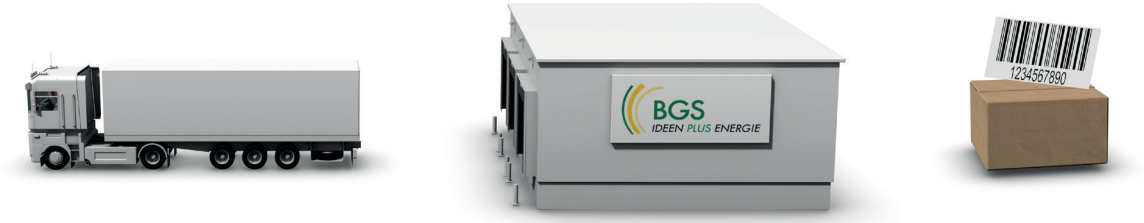
Clothing and accessories also reach us from all over the world. These products are often only microbially safe after radiation treatment. BGS gently, quickly and sustainably destroys germs from all kinds of products and everyday items - be it the stylish leather bag, the new body care line, the robust knife block for the kitchen or the delicate candleholder for the living room shelf.

IRRADIATION SERVICES IN THE LOGISTICS CHAIN

DEPENDING ON THE TYPE OF PRODUCT, the goods undergo one of two possible process variants during radiation sterilization. If the products are treated with gamma rays, they remain on the transport pallets due to the high degree of penetration depth. The fully automated conveyor system at BGS is aligned with industry and Euro pallets – here, maximum limits for dimensions and weight must be observed, which are defined in our delivery specifications. The plant control system ensures that each pallet completes the prescribed number of cycles in the system. In this way, the radiation dose is reproducible and is complied with upon each delivery of goods.

In the case of sterilization with electron beams, individual cardboard packages are irradiated due to the lower penetration depth of the radiation. The delivery specifications also must be observed here. The run through the irradiation unit in the facility itself only takes a few seconds. For this purpose, the cardboard packages are individually conducted on conveyor belts or cassettes through the facility -

1 In the application development, the optimal arrangement of the products in the process flow and the radiation dose are determined in advance and entered into the system.



2 Upon delivery, the products are labelled with a barcode and equipped with dosimeters at predefined positions.

withdrawal from the packing scheme does not take place at any time. Depending on carton dimensions and product arrangements in the carton, irradiation on two sides is required. This means that the cartons are turned over and conducted through the radiation field again to guarantee the most homogeneous dose distribution possible. After the treatment, the cartons are repacked in their original state in compliance with the packaging configuration.

What happens after irradiation?

After the irradiation process for the sterilization has taken place, the radiation dose applied is controlled with the help of the dosimeter attached to the product. If everything is in compliance with the specifications, quality assurance grants immediate approval – and the product is then ready for immediate use. In contrast to ETO sterilization, sterilization with rays does not require waiting times for degassing and approval tests. As long as the materials are suitable, irradiation using electron beams or gamma rays is therefore the best choice for time-demanding supply chains. The transport logistics to the end customers follows seamlessly. This results in huge advantages in terms of time and processing at reduced costs.

The usual processing time at BGS is between five and a maximum of ten working days. Depending on the volume of delivered goods and utilization, we state a probable pick-up date in each case. Following completion of each irradiation, the system automatically informs the customer about the definitive order for collection, irrespective of the time of day. This way, the customer can immediately arrange the further logistics and organise the collection of its goods. Documentation and certificates are part of each irradiation treatment, which are concomitantly available with the completion message.

What should be observed with regard to delivery and packaging?

For loading and unloading of the trucks, BGS has standard ramps at all three locations, which should be primarily used. It is important to discuss and coordinate deliveries and collections deviating from the standard during the preliminary stages, so that they can be integrated smoothly into the logistics process. In case of frequent delivery, packaging and pallets should be renewed regularly, as they lose their firmness if they are irradiated repeatedly, amongst other things. Our experts will be happy to offer advice about how frequently it makes sense to exchange the

3

Depending on the product, two process types are available for radiation sterilization: Gamma rays (above) or electron beams. In the process, the dose and duration of irradiation individually calculated for the product are applied to obtain sterility.

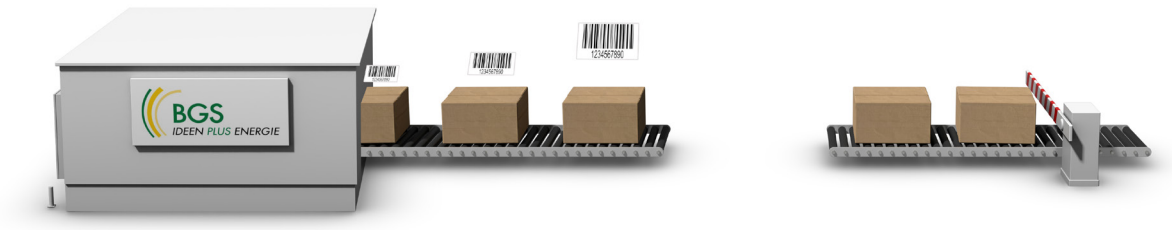
IRRADIATION SERVICES IN THE LOGISTICS CHAIN

respective type of packaging. Even seemingly small things must be taken into account. If, for example, the packaging is used frequently, care must be taken that the irradiation labels and indicator points on the packaging are completely removed after each treatment to avoid any mix-ups.

As a rule, the pallets have to be suitably stable for the automated processes in the irradiation routes. In the case of special pallets, it has to be verified in advance whether the format can be transported by the system at the location. The pallets will not be exchanged during the process and remain in possession of the customer. This makes the processing steps easier since forwarding agents do not have to provide substitute pallets, but can pick up the goods again in the same packaging scheme as delivered.

At which location is irradiation carried out?

We determine the location of irradiation in consultation with our customers. In addition to the transport routes, the type of product handling, facility-specific aspects and capacity utilization of the plants also play a role. All our irradiation facilities comply with the latest state of the art and are differently configured. In this way, a large range of products can be treated and a disruption of the facilities compensated. The principle of redundancy applies: Each loca-



4 Following irradiation, the radiation dose applied is checked and the barcode read out with the help of a dosimeter attached to the product.

tion is largely able to take over the products of the other locations. If unforeseen disruptions or machine failures occur or express requests are accepted, these can usually be absorbed by one of the other locations. In this way, we make an essential contribution to meeting the delivery commitments of our customers dependably and guarantee optimal planning reliability.

Location Wiehl (North Rhine-Westphalia)

The location in Wiehl has four electron accelerators with an energy field of 0.5 to 3.0 MeV and max. 150 kW. The plants are equipped with flexible handling systems for endless products such as cables, pipes, tubes as well as for the irradiation of piece goods such as cardboard packages and components. Wiehl is also the location of a 5 MCi cobalt-60 gamma plant, where Euro pallets and industrial pallets up to a height of 190 cm can be irradiated.

Location Bruchsal (Baden-Wuerttemberg)

Bruchsal has two electron accelerators with an energy field of 2.5 to 10.0 MeV, which can be used to irradiate endless products flexibly such as cables, pipes, tubes and piece goods such as cardboard packages and components. Since 2018, we have also operated an ultramodern 6 MCi cobalt-60 gamma plant in Bruchsal, where Euro pallets and industrial pallets up to a height of 190 cm can be irradiated. At this location, it is also possible to irradiate parts with dimensions of up to 12 metres in length and 1.60 metres in width, such as tube bundles and poles.

Location Saal a. d. Donau (Bavaria)

In Saal, a 10 MeV electron accelerator with a fully automated line for the acceptance and packing of Euro pallets enables the irradiation of large quantities with short turnaround times. In addition, a 5 MeV electron accelerator with variable acceleration voltage is available for the irradiation of endless products such as pipes, tubes, profiles and cables.

5 The products are now optimized ...

6 ... and ready for transport.

SERVICE AND CONSULTING

Sterilization with electron beams and gamma rays is usually an outsourced process that is carried out by specialised service providers such as BGS. This is because the operation and setup of such plants is complex and must meet the highest quality standards in compliance with strict regulatory requirements.

Operators of gamma plants and electron accelerators have to meet extremely high structural safety standards and be equipped with extensive monitoring technology, amongst other things. In practice, it is therefore rarely cost-efficient for manufacturers to operate their own irradiation facilities. Cooperation with a service provider who treats the products in special facilities in an outsourced process is recommended for a number of reasons: BGS has elaborately set up the comprehensive expertise required for irradiation over the course of four decades, and it always represents the current state of the art. All our processes are also highly automated due to capacity utilization and expertise, and ensure the

necessary speed and high quality standard in the processing. This pays off particularly in series production.

Depending on the area of application, the high-energy electron beams and gamma rays used at BGS convert the irradiated products precisely dosed into a sterile state or provide an upgrading of product properties in the area of radiation crosslinking. The great advantage of a treatment with ionising rays is that the products can be used or further processed immediately after a simple approval step (dosimetric release) – without further tests or storage and waiting times. It is important to plan all processing steps thoroughly between manufacturer and service provider right from the outset and to coordinate the workflows in detail so that the actual irradiation can be carried out efficiently. Once defined, the irradiation result is completely reproducible.

The process to be used depends on the irradiation goal. In the case of radiation sterilization, it is the damage caused to the DNA of microorganisms, which is equally achieved with electron beams and gamma rays. They die and reliably lose their ability to reproduce. With the help of test series in the run-up to irradiation treatment, it can be determined whether the bioburden is reduced in compliance with the regulations. In this context, besides factors like the radiation dose, the packing scheme also plays a decisive role, since in the series process later on, details such as packaging density, packing material, size of cartons, product alignment and product structure and/or composition are of major importance for efficient radiation.

QUALITY MANAGEMENT AND CERTIFICATION

At BGS, we use a stringent and sophisticated quality management system, which is being continuously developed. The quality management system of our company is certified in accordance with the standards ISO 9001, DIN EN ISO 13485 and EN ISO 11137.
BGS is also FDA registered and holds the JAPAN PAL certificate for all three locations, which is a prerequisite for the approval of medical devices in Japan.

Thanks to state-of-the art process technology and IT systems, we are able to provide highest standards of quality at BGS – without losing the flexibility for individual solutions. The plants at our three locations are configured differently in order to handle a wide range of products and satisfy various customer wishes. Nevertheless, the principle of “redundancy” applies: Each location is largely able to take over the processes of the other locations. In this way, we significantly contribute to failsafe reliability in the production and enable faster lead times.

We offer our customers direct and personal contact with our responsible specialists in the company. We are also happy to take on unusual challenges – and remain curious to further open up the endless and yet undiscovered potentials of irradiation together with users.

All our processes are highly automated due to capacity utilization and expertise, and ensure the necessary speed and high quality standard in the processing.

PLEASE CONTACT US AT:

BGS BETA-GAMMA-SERVICE
GMBH & CO. KG

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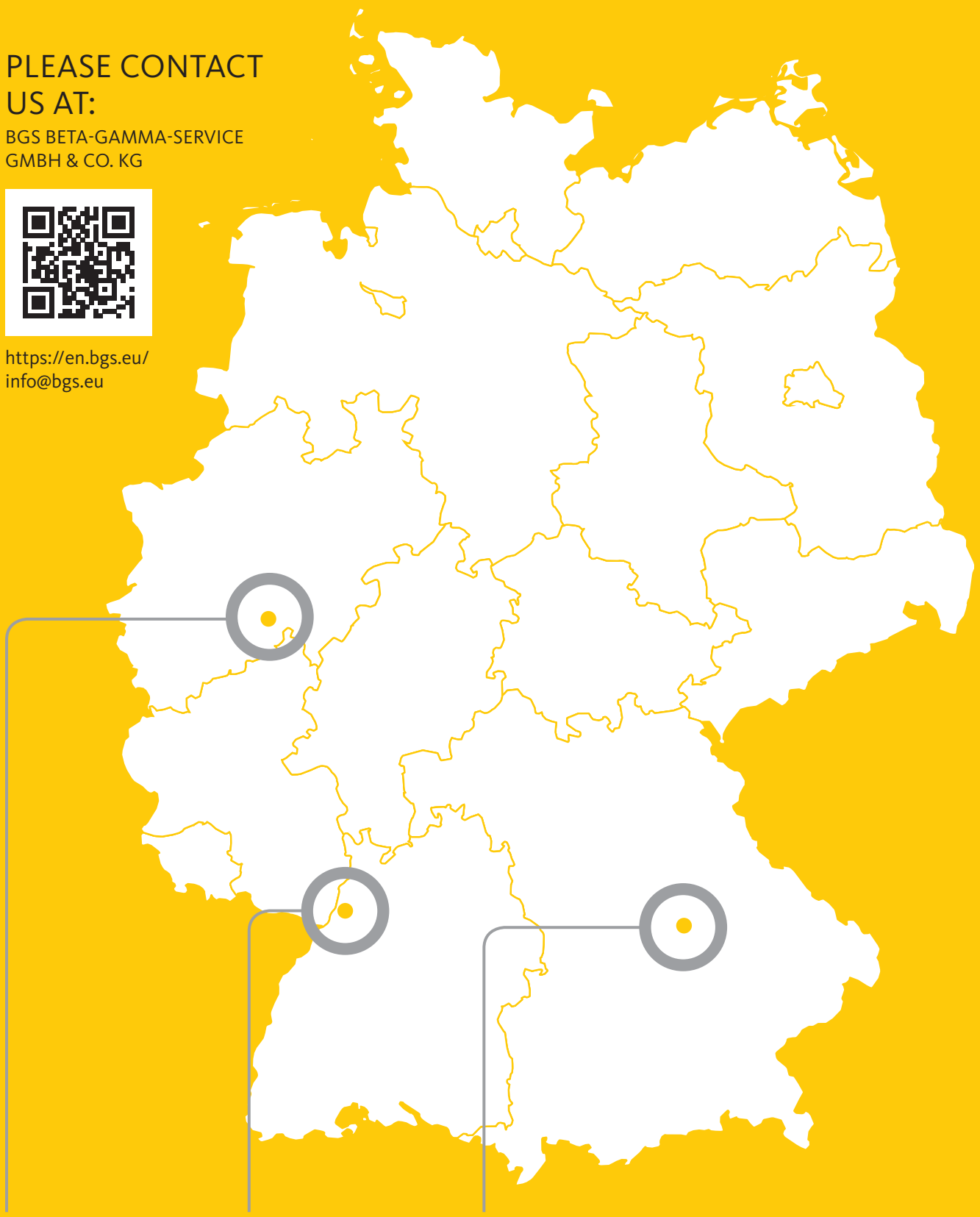

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