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Review Article

Theme: Sterile Products: Advances and Challenges in Formulation, Manufacturing, Devices and Regulatory Aspects
Guest Editors: Lavinia Lewis, Jim Agalloco, Bill Lambert, Russell Madsen, and Mark Staples

Reducing the Risk of Contamination of Sterile Parenteral Products via Ready-to-Use Closure Components

Wayne Curry,[1,2] Samuel Conway,[1] Clara Goodfield,[1] Kimberly Miller,[1] Ronald L. Mueller,[1] and Eugene Polini[1]

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Abstract. The preparation of sterile parenteral products requires careful control of all ingredients, materials, and processes to ensure the final product has the identity and strength, and meets the quality and purity characteristics that it purports to possess. Contamination affecting these critical properties of parenteral products can occur in many ways and from many sources. The use of closures supplied by manufacturers in a ready-to-use state can be an effective method for reducing the risk of contamination and improving the quality of the drug product. This article will address contamination attributable to elastomeric container closure components and the regulatory requirements associated with container closure systems. Possible contaminants, including microorganisms, endotoxins, and chemicals, along with the methods by which these contaminants can enter the product will be reviewed. Such methods include inappropriate material selection, improper closure preparation processes, compromised container closure integrity, degradation of closures, and leaching of compounds from the closures.

KEY WORDS: component preparation; container closure integrity; plungers; sterilization; stoppers.

INTRODUCTION

The US Food and Drug Administration (FDA) Guidance for Industry: Container Closure Systems (CCS) for Packaging Human Drugs and Biologics (1) establishes that, "Every proposed packaging system should be shown to be *suitable* for its intended use: it should adequately *protect* the dosage form; it should be *compatible* with the dosage form; and it should be composed of materials that are considered *safe* for use with the dosage form and the route of administration."

Failure to meet any of these criteria can cause a drug product to be contaminated. Examples of failures include:

- Not protecting—allowing water vapor ingress to a lyophilized drug vial
- Incompatibility—loss of safety and drug potency due to a leachable from the elastomer
- Not safe—introduction of microorganisms or endotoxins into the drug product

These contaminants can enter the product through many methods, including:

- Inappropriate materials of construction
- Improper closure preparation processes
- Compromised container closure integrity
- Degradation of closures and leaching of compounds from the closures

These regulations place a very high standard on the elastomeric container closures (referred to here as closures), which are part of the CCS for a given drug. To achieve this standard, a thorough knowledge of elastomer science, pharmaceutical technology and regulatory requirements is required to design, manufacture, and prepare closures for use with sterile injectable products. Collaboration with closure suppliers and the use of closures supplied in a ready-to-use state can be an effective method for reducing the risk of contamination and improving the quality of the sterile drug product.

REVIEW OF REGULATORY REQUIREMENTS CONCERNING ELASTOMERIC CLOSURES

Although the regulations and associated guidance documents rarely provide direct instructions on how to select and prepare packaging components, regulatory documents from around the globe provide a framework for validation and testing requirements, as well as information pertaining to closures that needs to be included in the drug application (1–5). Table I, Regulatory Reference Guide for Preparation of Parenteral Packaging Components, summarizes frequently cited regulatory documents. Thoroughly understanding and establishing processes to meet all of these requirements is critical to minimizing the risk of contamination attributable to the CCS. Monitoring the publications of regulatory sources for new and changing rules is vital to maintain compliance.

[1] West Pharmaceutical Services, Inc., Lionville, PA, USA.
[2] To whom correspondence should be addressed. (e-mail: Wayne_Curry@westpharma.com)

Table I. Regulatory Reference Guide for the Preparation of Parenteral Packaging Components

	Code of Federal Regulations Title 21, Chapter I, Part 211—Current Good Manufacturing Practice for Finished Pharmaceuticals	FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics	FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing	FDA Guidance for Industry: Documentation for Sterilization Process Validation	USP	EudraLex Vol 4 EU GMP, Annex 1 Manufacture of Sterile Medicinal Products	Why it's important
Suitability for intended use		III.A, III.B.1					Information intended to establish suitability including an adequately detailed description of the tests, methods, acceptance criteria, reference standards and validation information studies should be provided in the drug application
Bioburden	211.160(b)(1)(2), 211.80(b), 211.84(D)(6), 211.113(B), 211.94(C)		Section VIA., VI.B.1 and VII	II.C,1,2(pp 5,6); II.D (p 7); II.H (p 8)		31, 34, 74, 77, 83, 98, 125	Bioburden on stoppers can lead to contamination of drug products. Maintaining microbiologically clean components is critical to preventing contamination and preserving drug product integrity during storage, shipping and handling. FDA requires each lot of closures to be tested for microbiological contamination. Sterilization processes should not be deleterious to closures
Pyroburden	211.94(c)(d), 211.160(b)(1)(2), 211.80(b), 211.167(a), 211.84(D)(6)		Section VIA., VI.B.1 and VII	II.D(p7); II.F & II.H (p 8); IV.C (p 12)	<85>		Pyroburden (levels of biological endotoxin) on stoppers can contaminate and compromise the drug product. FDA requires each lot of closures to be tested for microbiological contamination. FDA requires validation of a minimum 3-log reduction during initial product validations
Particulate	211.160(b)(1)(2), 211.80(b)				<788>	31, 77,	Particulate on stoppers can be transferred to packaged drug products causing particles in the drug. This can lead to end-of-the-line rejects and could cause major problems for

			complex protein and peptide drug products. Maintaining particulate-clean stoppers, once washed, is critical to preventing contamination during storage, shipping and handling of packaged drug products
Cleaning	211.63, 211.65(a), 211.67, 211.182, 211.80(b)	Section VII	A validated cleaning process prevents item-to-item contamination and process variability of silicone, particulate matter, bioburden and endotoxin

OVERVIEW OF ELASTOMER TECHNOLOGY

A basic understanding of elastomer technology is necessary to understand the value that closures bring to the drug product and the potential risks of contaminating the drug as a result of improper closure selection and processing.

Elastomers are formally defined as materials that can be stretched to twice their original length and quickly return to their original dimension without permanent deformation (6). Elastomers are ideal materials for closure systems for rigid-walled containers because they can maintain the compressive force generated when sized to provide proper interference fit and crimped in place on the vial. The compressive force combined with the material's ability to conform to small voids, imperfections and fissures on the mating (contacting) surface of the container protects the drug product for extended periods of time under various environmental conditions. In addition to sealing to the vial, these materials have the ability to reseal after repeated penetrations with various types of cannulas, preventing the generation of a pathway for contamination that may harm the contents of the package (7).

The recipe for the elastomer formulation typically consists of polymer(s), curing and accelerating agents, filler (s), processing aids, antidegradants and plasticizers, and can be optimized to function properly for the specific application (8). Residual chemicals or additives in the elastomeric matrix may migrate into drug product that is in contact with the closure due to chemical affinity and diffusion characteristics. Adsorbtion and/or absorption may also occur between the drug solution and the closure. That is why it is important to formulate the elastomer with ingredients having low toxicity and in quantities that will minimize unreacted residuals in the elastomeric matrix. It is also important to understand the migratory behavior of chemical ingredients so some prediction of interaction can be made before final container closures are selected (7).

Butyls and halobutyls are the most commonly used elastomers for parenteral pharmaceutical closures and are excellent for long-term parenteral storage due to the low diffusion of various gasses through the elastomeric matrix. These polymers are particularly suitable for long-term parenteral storage because of their ability to retain headspace of inert gasses over a drug product and prevent the ingress of atmospheric oxygen which could oxidize the drug and render it ineffective. In addition to providing good oxygen protection, butyls/halobutyls also provide a good barrier to water vapor transmission. Water vapor can migrate through the rubber septum and damage the product if the proper elastomer matrix is not used. This is critical when packaging products subject to hydrolysis or hygroscopic solids and liquids. Cleaner vulcanization systems can be used with butyls/halobutyls, which reduces the potential extractables from the elastomeric matrix. Butyls/halobutyls demonstrate reduced physical properties, such as resistance to fragmentation and resealability, and for this reason may not be an ideal choice for high multidose applications.

Elastomeric closures produced from polyisoprene polymers (either natural rubber or synthetic) provide excellent resealability and good resistance to radiation and for this reason are typically selected for applications that have

demanding physical or functional requirements. However, consideration must be given to the higher level of extractables, cytotoxicity, and poor barrier properties of polyisoprene and natural rubber polymers. Halobutyl can be blended at varying ratios with polyisoprene to provide an elastomeric closure that can balance the positive and negative properties of these two polymers.

Other polymers, such as silicone, ethylene propylene diene monomer, nitrile, neoprene, and styrene butadiene rubber are also used in very low volumes for a variety of niche applications.

Closures are manufactured in a wide variety of designs that fall into the following categories:

- Serum stoppers—utilized for liquid and powder preparations, typically sized 13 or 20 mm with a cupped plug design.
- Lyophilization stoppers—specifically used for freeze-drying processes, typically sized 13 or 32 mm with a longer vented plug design permitting sublimation drying prior to capping and sealing.
- IV stoppers—used for large-volume IV containers, designed to allow both easy insertion of the spike and retention of the spike over the full infusion time; typical size 28–32 mm.
- Syringe/cartridge pistons—for pre-fillable syringe and cartridge systems, multi-ribbed pistons are designed to seal tightly to the syringe barrel during storage and movement to inject the fluid through the cannula.

CLOSURE SELECTION

Selection of a closure is a combination of the design and material with the goal of achieving chemical compatibility with the drug product, functionality as intended and container closure integrity over the drug product's shelf life (7).

When selecting the material for the closure, consideration must be given to the characteristics of the drug, including solvent vehicle and pH, preservatives, buffers, and any other known drug product sensitivities. An understanding of these attributes affords a higher success rate regarding compatibility of the drug/closure combination and reduces the risk of unwanted interactions between the closure and product, especially those not apparent early on. Long-term chemical compatibility is ultimately demonstrated through extractable/leachable studies, which are generally performed as part of drug product stability testing.

At the point of use, the closure should not fragment from needle penetration, and the needle penetration force must be low. If the drug product is intended for multiple dosing, then the closure must be able to reseal to prevent contamination over its shelf life.

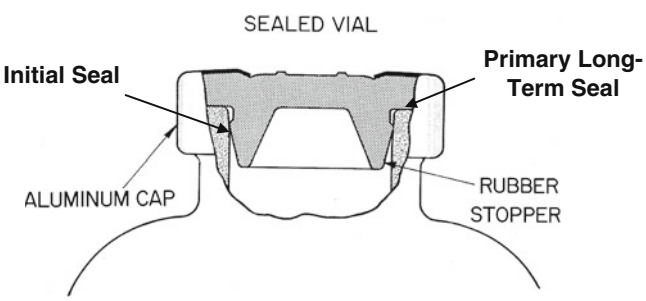

Fig. 1. Sealed Vial

Container closure integrity is vital to protecting the dosage form over its shelf life. The long-term seal is formed by the aluminum crimp compressing the bottom of the stopper flange to the top surface of the vial crown. However, prior to the application of the aluminum crimp, the seal provided by the interference fit (typically 2–10%) of the stopper plug in the vial bore must provide an initial seal (see Fig. 1 Sealed Vial). This seal prior to crimping is especially important in the freeze-drying process where it acts as the only seal to maintain vacuum during transport from the lyophilization chamber until the aluminum crimp seal is applied (9). Optimal compression of the elastomer coupled with stopper/vial fit is critical to achieve container closure integrity.

PREPARATION PROCESSES—WASHING

The major goal of elastomer closure preparation is the removal of two types of contaminants: bacterial endotoxins and particles. There are three ways to remove endotoxins: heat, chemical, and rinsing. The temperature and duration required for the heat method will damage the elastomeric closures and render them unusable. Residuals from the chemical methods can leach into the drug products and negatively affect the purity of the drug product. This leaves rinsing as the most appropriate method.

The FDA Aseptic Processing Guidance (2) states, "Rubber closures can be cleaned by multiple cycles of washing and rinsing prior to final steam or irradiation sterilization. At minimum, the initial rinses for the washing process should employ at least purified water, USP, of minimal endotoxin content followed by final rinse(s) with water for injection (WFI) for parenteral products. Normally, depyrogenation can be achieved by multiple rinses of hot WFI." The Guidance recommends a validation study using closures spiked with a known quantity of endotoxins, demonstrating the depyrogenation process reduces endotoxins by at least 99.9% (three logs). This process of multiple cycles of washing and rinsing is also effective in reducing the particulate load on the stoppers. Frequently, a detergent is added to the initial cycle to aid in particle removal, but must be adequately rinsed from the stoppers during the subsequent steps. In addition, the wash process is frequently used to apply silicone oil to the closures by adding it to the final rinse cycle. Silicone oil is a possible source of particulate and/or endotoxin contamination and should be controlled to assure it does not have an adverse effect on the drug product.

PREPARATION PROCESSES—STERILIZING

The Code of Federal Regulations Title 21 clearly establishes the requirement for components of container closure systems to be sterilized to be safely used for their end application. The perfect sterilization process would be one that destroys all microorganisms rapidly without adverse impact on any of the material's essential properties (10). Unfortunately, due to the harsh conditions required to

destroy microorganisms and the need to maintain the material properties previously discussed, this perfect process does not exist for most elastomer materials. Therefore, the selection of both the method of sterilization and the specific process parameters should be evaluated for the risks associated with closure compatibility.

Common sterilization methods include moist heat (*i.e.*, steam), dry heat, ionizing radiation (gamma or e-beam) and gas (typically ethylene oxide). Dry heat requires temperatures and duration well beyond the service conditions of typical pharmaceutical elastomers and is not a viable option. Gasses are frequently used for medical devices but are not commonly used for pharmaceutical applications due to concerns with residuals affecting the purity of drug products. Moist heat and ionizing radiation are commonly used but have pros and cons that should be examined on a case-by-case basis.

Moist heat is the most common method used for sterilizing vial closures. The process is typically performed in an autoclave under saturated steam conditions at the drug filling facility, placing full control and responsibility of the process on the drug manufacturer. Component manufactures have recently introduced ready-to-use products sterilized by steam, reducing regulatory burden and improving process efficiency while minimizing the risk that the change would adversely affect previously established stability data since the process is essentially the same. Common exposure parameters are 121–122°C for 30–60 min. The process must go through a rigorous validation program, which is described in detail in the PDA Technical Report No.1 Validation of Moist Heat Sterilization Processes (11).

Many factors can impact the effectiveness of the process to destroy the microorganisms and must be considered in the validation program. These factors include, among others:

- Qualification of the equipment
- Resistance (D) value of the material to be sterilized
- Thermal profiling of the chamber
- Heat penetration of the load
- Load sizes and configuration
- Use and placement of biological indicators
- Air removal

Ionizing radiation (both electron beam (e-beam) and gamma radiation) have become effective and useful tools in the manufacture of parenterals. In particular, gamma radiation has been used for many years to sterilize pistons used in pre-fillable syringe systems and has also seen limited use with vial closures. Due to safety and radiation containment concerns, gamma irradiation is virtually always performed by a third-party sterilization facility. While the sterilization facility will certify compliance to cGMPs and that the product received the specified irradiation dosage (typically 15–50 kGy), they will not take responsibility for validating that the dosage is sufficient to sterilize the product properly. This must be done either by the pharmaceutical company or, in the case of ready-to-use components, the supplier of those products. PDA Technical Report No. 11 Sterilization of Parenterals by Gamma Radiation (12) and ANSI/AAMI/ISO 11137 1–3 standards (13–15) provide methodology for validating the sterilizing dosage. Since the sterilization is performed at a different site than the filling of the drug containers, the system used to package and method for transporting the closures from the sterilizer's site to the drug filling site must also be validated to maintain sterility.

In addition to assuring sterility, the validation program should demonstrate that closures processed by any sterilization method still have the proper physical and chemical properties to maintain the quality and efficacy of the drug product over its shelf life. All of this information is typically included as part of the Chemistry, Manufacturing and Controls section of regulatory filings.

EFFECT OF STERILIZATION ON PHYSICAL PROPERTIES OF ELASTOMERIC CLOSURES

As previously stated, moist heat and radiation are the primary methods used to sterilize closures. Both can affect the physical properties of the closures but unlike other methods of sterilization, irradiation can generate free radicals in the polymeric materials and has the potential to cause a greater compromise of properties. Gamma photons or electrons released to yield lethal bioburden doses can simultaneously deliver sufficient energy to excite and dissociate polymer chain bonds. As a result, this ionizing energy produces free radicals within a polymer structure that may then undergo a series of perpetual cross-linking reactions in an attempt to regain its original structural stability (16,17). Post irradiation, these reactions can occur over a period of months, resulting in polymer chain grafting, changes in polymer backbone saturation, chain scission, oxidation, isomerization, and/or crystallization. The heat from steam sterilization can also potentially initiate cross-linking reactions but once the heat cycle has ended, the reactions will cease.

Radiation exposure can impact the physiochemical properties of polymeric components. As previously stated, radiation reacts with polymers to promote chain scission or cross-linking. The breaking and formation of chemical bonds within polymeric components can detract from their performance (18). Typically in cross-linking reactions, tensile strength, hardness, modulus, and compression set are increased while elongation is reduced. On the other hand, scission reactions have the opposite effect on the aforementioned properties. The effect of irradiation on common polymers used for pharmaceutical applications is shown in Table II. Additionally, an increase in concentration and nature of the polymer extractable profile can be altered as a function of scission reactions.

Reactions similar to those taking place to cure the closure during the molding process can be initiated by steam sterilization, but the temperatures during steam sterilization are lower than molding temperatures so the reactions occur at a much slower rate. Unless excessive temperatures and times are used for the steam sterilization cycle, the effects on physical properties are minimal (19,20).

Inhibitors and stabilizers are added in small amounts to polymer formulations to offset the effect of degradation during exposure. These materials are designed either to absorb energy or react with free radicals generated during radiation processing. Aromatic polymers are generally more resistant to radiation effects than aliphatic polymers. The

Table II. Radiation Tolerance Levels of Polymers Used for Medical Applications

Material	Tolerance (kGy)	Comments
Butyl	50	Sheds particulate after irradiation
Polyisoprene	100	Very stable with sulfur or resin cure systems Avoid stressing product by not bending, folding or wrinkling in package
Ethylene propylene Diene monomer	100–200	Cross-links; yellows slightly
Fluoroelastomer	50	Avoid multiple sterilization
Nitrile	200	Avoid multiple sterilization
Silicones	50–100	Cross-link density increases more in peroxide systems than in platinum systems. Silicones retain a slight memory of coiling shape in packaging
Styrene butadiene	100	Avoid multiple sterilization

Excerpted from Sterigenics: Material Considerations—Irradiation Processing (21)

degree of radiation resistance of an aliphatic polymer is directly proportional to its degree of saturation and/or substitution. Additionally, thin component cross-sections are more susceptible to oxidation than thicker ones. This is due to higher oxygen exposure during the irradiation process leading to degradation (16).

EFFECT OF STERILIZATION ON CHEMICAL PROPERTIES OF ELASTOMERIC CLOSURES

The sterilization process transfers a significant quantity of energy (heat or radiation) into the elastomer material that can initiate a variety of chemical reactions. These reactions have the potential to change the quantity of compounds present in the closures and/or create new compounds. Either of these outcomes can change the extractable/leachable profile of the closure.

To investigate what effect sterilization can have on the extractable profile of closures, a study was performed in which the extractables profile of two different butyl rubber formulations was characterized before and after closures had been sterilized by steam (30 min at 121°C) and by irradiation at two different energy levels (20 and 40 kGy). These samples were subjected to a battery of extraction and chromatographic methods to establish their extractable profiles. The results indicate that steam sterilization had little effect on the extractables profile, other than a slight decrease in the content of antioxidant butylated hydroxytoluene (BHT). Irradiation had a greater effect. The amount of elemental sulfur present was reduced to undetectable levels with a concurrent increase in the levels of water-soluble sulfur, likely in the form of carbon disulfide, which was detected by headspace analysis. Extraction of antioxidant BHT was likewise reduced in the irradiated samples, with the smallest quantity of extracted BHT found in the sample irradiated at the highest energy level. Irradiation also increased the number of components identified as fragments of the polymer backbone, with the highest number of fragments detected from the sample irradiated at the highest energy level. The GC/MS chromatographs of the dichloromethane extract shows the increased number of peaks associated with these fragments and are presented in Fig. 2, extractable profiles. Acetone was detected in the headspace over all irradiated samples, but not over the steam-sterilized or control samples. These results were consistent with expectations based on the ingredients in these formulations.

CHANGING ROLES OF CLOSURE MANUFACTURERS AND PHARMACEUTICAL COMPANIES

The risk of contamination from elastomeric closures can be eliminated or reduced to acceptable levels through the application of a thorough knowledge of elastomer science, pharmaceutical technology, and regulatory requirements to design, manufacture, and prepare closures for use with injectable products. Historically, this knowledge has been split between the closure suppliers' understanding of elastomers and the drug manufacturers' understanding of the regulatory and pharmaceutical process aspects. More recently, two key drivers are fostering change in the responsibilities of closure and drug manufacturers: (1) new pharmaceutical compounds that are increasingly sensitive to various forms of contamination and (2) the desire of pharmaceutical companies to outsource services they no longer consider core competencies.

Closure manufacturers have had the opportunity to work with pharmaceutical manufacturers to gain a more in depth knowledge of pharmaceutical processes as well as instituting the appropriate regulatory framework which has resulted in suppliers now offering complete drug packaging solutions instead of merely components. Extractable/leachable analytical studies and ready-to-sterilize and ready-to-use components are examples of this expanded role. The suppliers' intimate knowledge of the materials makes them highly qualified to design and validate stopper preparation processes that fully comply with regulatory expectations while having minimal affect on the chemical and physical properties and to characterize these effects fully.

Specifically, the suppliers' deep understanding of the details of the polymer(s), cure systems, and additives of the closures puts them in a unique position to understand the potential for deterioration of the physical properties and changes to the extractable/leachable profile caused by the sterilization process. This provides the suppliers the ability to develop customized sterilization processes and tightly control the truly critical sterilization process parameters of their ready-to-use products to minimize the risk of the closures

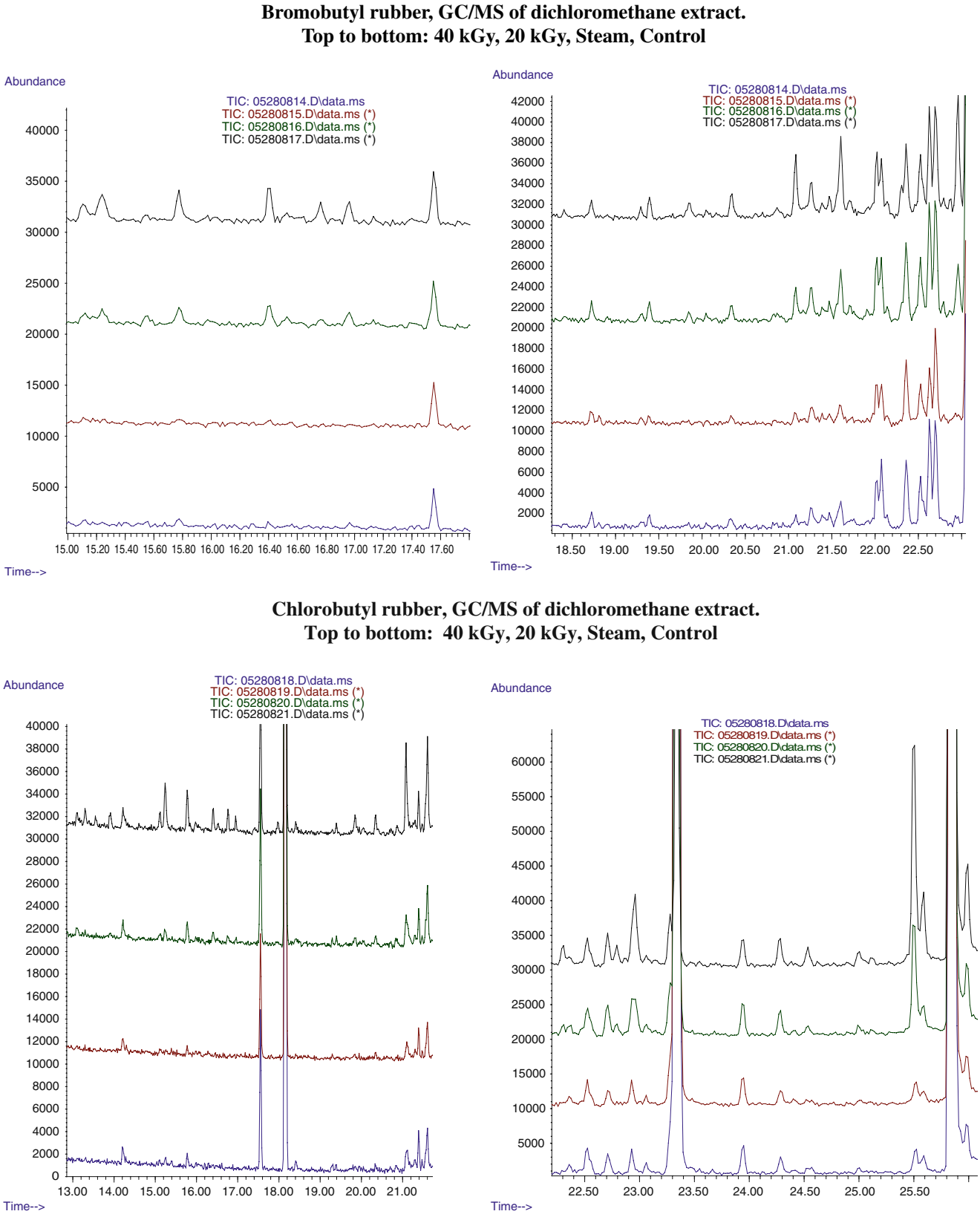

Fig. 2. Extractable profiles. Bromobutyl rubber, GC/MS of dichloromethane extract. *Top to bottom* 40 kGy, 20 kGy, steam, control. Chlorobutyl rubber, GC/MS of dichloromethane extract. *Top to bottom* 40 kGy, 20 kGy, steam, control

contaminating the final drug product. Further, due to the high level of impact on the closure manufacturing business, they have a keen interest in keeping abreast with changes to regulations that relate to containers and closures and frequently take the position of advocate for the pharmaceutical industry with agencies around the globe.

CONCLUSION

Drug products can be contaminated through the container closure in many possible ways. It is clear that knowledge of the characteristics of both the container closure system and the drug product is required to maintain the optimium quality level of the drug over time. By utilizing a closure manufacturer's available solutions, including ready-to-use products and collaborating with technical and regulatory experts, pharmaceutical manufacturers can obtain the lowest possible level of risk from any form of contamination related to the closures, thus improving the safety and efficacy of the drug product throughout its shelf life.

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