MediZap
Advanced Sterilization

# Terminal E-Beam Sterilization and Dosimetric Release for 503A and 503B Compounding – Regulatory Analysis

www.medizap.co 3341 Swetzer Court, Loomis, CA 95650 +01.775.386.6677

MediZap
Advanced Sterilization

## 1. Executive Summary

Many compounded sterile preparations (CSPs) are currently sterilized by aseptic filtration and released after a **USP <71> sterility test**. The *revised* USP <797> limits batch size for CSPs requiring sterility testing to **250 units** and still requires a 14-day sterility test. However, **E-Beam irradiation** can terminally sterilize finished CSPs and achieve a sterility assurance level (SAL) of **≤ $10^{-6}$,** ten to 100 times more stringent than the SAL achieved with steam or dry-heat sterilization. Under ISO 11137-1/2 and ISO 11737-1/2, E-Beam processes are validated and monitored through **bioburden determination**, **dose-setting studies,** and **routine sterilization-dose audits**; ISO 11737-2 explains that sterility testing on products exposed to a complete terminal sterilization cycle provides **no scientifically usable data and is not recommended**. USP <71> itself states that sterility procedures "are not by themselves designed to ensure that a product or batch is sterile or has been sterilized" and that sterility assurance must come from **validation of the sterilization process or aseptic processing procedures**.

This analysis argues that **dosimetric (parametric) batch release**—where each batch is released based on dose delivery and compliance with validated process parameters—meets or exceeds the sterility assurance of USP <71> sterility testing for E-Beam-sterilized CSPs. ISO 11137 requires routine **dose audits** that examine bioburden levels, microbial resistance, manufacturing process controls, and the margin between the processing dose and the sterilization dose. When these audits show the validated sterilization dose continues to achieve an SAL of $10^{-6}$, the sterile product can be released based solely on dose measurements (dosimetry) and critical process parameters. This approach eliminates the 14-day sterility test and supports larger batch sizes, enabling production runs beyond 250 units while maintaining (or improving) sterility assurance.

## 2. Regulatory Background and Requirements

### 2.1 Statutory Framework for 503A and 503B Entities

- **503A pharmacies** are traditional compounders that prepare patient-specific prescriptions. They are exempt from certain sections of the federal Food, Drug, and Cosmetic Act but must comply with **State Board of Pharmacy rules** and **USP <797>**. The revised USP <797> limits the batch size for CSPs requiring sterility testing to **250 units**, as manual compounding increases the risk of contamination and larger batches decrease the likelihood of detecting contamination. 503A compounders must perform sterility testing on batches with beyond-use dates (BUDs) that require it and perform **endotoxin testing**.
- **503B outsourcing facilities** may be used for office purposes and distributed interstate. They are subject to the FDA's **current good manufacturing practices (CGMP)** and are inspected by the FDA. Unlike 503A facilities, 503B facilities are not subject to the 250-unit cap because CGMP allows large-scale batch processing. They must validate and continue sterilization processes testing, monitor environmental controls, and test finished products (potency, endotoxins) as part of a comprehensive quality system.

### 2.2 Applicable USP Chapters

- **USP <797> (Pharmaceutical Compounding—Sterile Preparations)** sets minimum standards for sterile compounding. The chapter requires environmental controls, personnel training, beyond-use dating, and sterility/endotoxin testing when CSPs are prepared from non-sterile components or when BUDs exceed specified limits. It does **not prohibit the use of alternative technologies**; the introduction and scope section states that the use of technologies, techniques, materials, and procedures not explicitly covered is allowed when they are validated for their intended purpose and do not bypass safety requirements.

- **USP <71> (Sterility Tests)** prescribes methods for detecting viable microorganisms in sterile products. USP <71> notes that the compendial procedures **are not designed to ensure sterility of an entire batch** and that sterility assurance is achieved primarily through **validation of the sterilization or aseptic process**.
- **USP <85> (Bacterial Endotoxins Test)** establishes endotoxin limits and testing methods using Limulus Amebocyte Lysate (LAL).
- **Other USP chapters**, such as **<1223>** and **<1225>**, guide the validation of *alternative analytical procedures* and compendial procedures. These chapters are relevant for validating E-Beam dosimetry and bioburden tests.

### 2.3 ISO Standards for Radiation Sterilization

- **ISO 11137-1/11137-2** defines the requirements for the development, validation, and routine control of radiation (including E-Beam) sterilization. They describe methods for **establishing the sterilization dose** (Methods 1, 2, and VDMax) based on product bioburden and require routine **sterilization-dose audits** to verify that the established dose continues to achieve the desired SAL. Section 12.1.3 of ISO 11137-1 specifies that the interval between sterilization-dose audits may be **three months** or longer when a risk-based rationale is documented; the rationale must consider factors such as the specified bioburden limit, microbial resistance, method used to establish the dose, difference between processing dose and sterilization dose, materials of construction, manufacturing process controls and interval between batches.
- **ISO 11737-1** details methods for determining the population of microorganisms (bioburden) on products. Accurate bioburden data are needed for dose establishment and dose audits.
- **ISO 11737-2** covers sterility testing of products used to establish or audit a sterilization dose; however, the introduction cautions that **product subjected to the full terminal sterilization process has a very low probability of containing a viable microorganism** (e.g., 1 CFU, SAL $10^{-6}$) and that **performing a sterility test on such product provides no scientifically usable data and is not recommended**. This reinforces the regulatory basis for **parametric release**.

### 2.4 FDA Guidance and Precedent

The FDA has accepted terminal sterilization for human and veterinary drug products since 1994, as reflected in guidance on sterilization process validation that applies to radiation sterilization as well as other modalities. Radiation (electron-beam, x-ray, gamma) is listed as an accepted terminal sterilization method; the guidance outlines necessary controls, including facility and process design, packaging configuration, dose mapping studies, and microbiological methods. The agency recognizes ANSI/AAMI/ISO 11137, Parts 1–3, as consensus standards for radiation sterilization and expects compounding pharmacies and outsourcing facilities to validate their sterilization processes accordingly. Unlike moist-heat parametric release guidance, there is no FDA guidance specifically addressing the parametric release of radiation-sterilized products; therefore, firms should rely on ISO 11137 and USP 1222.

## 3. Dosimetric Release vs. Lot-Based Sterility Testing

### 3.1 Limitations of USP <71> Sterility Testing

1. **Statistical inadequacy** – USP <71> tests small samples (e.g., 20 units) from a batch. As the batch size increases, the probability of sampling a contaminated unit decreases. USP FAQs estimate that the probability of detecting contamination drops from 10% for 10–100 units to only 4% at 250 units and 2% at 500 units.
2. **Time-consuming** – USP <71> requires a 14-day incubation, delaying release and potentially leading to drug shortages.
3. **Limited assurance** – USP <71> procedures are not designed to ensure that an entire batch is sterile; sterility assurance must be obtained through process validation. Even a "sterile" result only indicates that the sampled units did not exhibit growth at the time of testing.

### 3.2 Principles of Dosimetric (Parametric) Release

1. **Validation of sterilization dose** – Under ISO 11137-2, the sterilization dose is established using the product's bioburden and microorganism resistance. Methods such as VDmax25 or VDmax15 involve fractional doses and sterility tests on test samples to determine the dose that achieves SAL $10^{-6}$.
2. **Routine dose audits** – ISO 11137-1 requires routine audits to confirm that the validated dose continues to achieve the desired SAL. The interval between audits must be either **three months** or justified by a rationale that considers bioburden data, microorganism resistance, processing parameters, and material controls. Audits involve measuring the product's bioburden and performing verification dose experiments on audit samples.
3. **Dose monitoring and dosimetry** – Each production batch is monitored by placing dosimeters on or within product loads and verifying that the measured dose is within the validated range. Process control records confirm that critical parameters (beam energy, conveyor speed, load pattern) were within specifications.
4. **Bioburden monitoring** – Routine determination of product bioburden ensures that it remains within the limits used in the dose-setting study. If bioburden increases, dose audits may be performed more frequently.
5. **Parametric release** – When dosimetry indicates that the product received at least the minimum sterilization dose and all validation parameters remain within control limits, the batch is released without performing USP <71> sterility testing. ISO 11737-2's introduction notes that performing a sterility test on a fully sterilized product provides **no scientifically usable data and is not recommended**. FDA guidance states that parametric release provides greater assurance of sterility than finished-unit testing because the probability of a non-sterile unit after terminal sterilization is extremely low ($\leq 10^{-6}$).

### 3.3 Comparative Advantages of Dosimetric Release

- **Greater assurance of sterility** – Terminal E-beam irradiation validated to SAL $10^{-6}$ yields a lower probability of viable microorganisms than aseptic processing or steam sterilization, which often achieve SAL $10^{-4}$. The Medizap analysis explains that grouping these modalities ignores the fact that irradiation delivers a significantly higher SAL.
- **Faster release** – Dosimetric release eliminates the 14-day sterility test, allowing products to be released almost immediately after irradiation.
- **Reduced cost and waste** – Fewer test samples are destroyed, and inventory carrying costs are lower.
- **Enables larger batch sizes** – Because sterility assurance derives from process validation rather than sampling, batch size is not constrained by the 250-unit sampling limit. This is particularly important for 503B outsourcing facilities.

## 4. Testing Obligations for 503A vs. 503B with E-Beam Terminal Sterilization

### 4.1 Sterility Testing

- **503A** – Under revised USP <797>, Category 1 and 2 CSPs require sterility testing when compounded from non-sterile components or when the BUD extends beyond specified limits. However, for CSPs terminally sterilized by validated E-Beam irradiation, parametric release is justified; ISO 11737-2 states that sterility testing provides no scientific value for such products. State Boards should accept dosimetric release if the pharmacy performs routine dose audits and documents dose delivery. In such cases, the 250-unit cap tied to sterility testing (see Section 5) does not apply.
- **503B** – FDA guidance and CGMP allow parametric release of terminally sterilized drug products. Outsourcing facilities must validate the sterilization process under ISO 11137, conduct routine dose audits, monitor bioburden, and document dose measurements. They may still perform periodic sterility tests as part of stability or media-fill studies, but sterility testing is not necessary for batch release.

### 4.2 Endotoxin Testing (USP <85>)

- **Requirement** – Endotoxin (bacterial pyrogen) testing is separate from sterility testing. USP FAQs clarify that CSPs administered epidurally should have the same endotoxin limits as intrathecal injections, as they may be infused over long periods. Moreover, BUDs requiring sterility testing **must** undergo endotoxin testing.
- **Impact of terminal sterilization** – E-beam irradiation does **not destroy endotoxins**, so validated endotoxin testing per USP <85> remains necessary for both 503A and 503B facilities. Endotoxin results must comply with USP limits based on the route of administration.

### 4.3 Potency (Assay) Testing

- **503A** – USP <797> requires that each CSP be compounded to meet its labeled strength, but routine potency testing is generally not mandated. Many 503A pharmacies voluntarily perform potency and stability testing to ensure quality. For example, a 503A pharmacy (VLS Pharmacy) explains that "potency over time" assays measure the strength of the medication using validated methods, such as **high-performance liquid chromatography (HPLC),** and that USP <1075> requires the assignment of beyond-use dates. When E-Beam irradiation is used, potency testing ensures that the radiation does not degrade the active ingredients. HPLC or equivalent assays should be validated per USP <1225>.
- **503B** – CGMP requires potency (assay) testing of each batch to verify that the active pharmaceutical ingredient (API) content is within specification. Outsourcing facilities must validate analytical methods, often employing HPLC, and must perform stability studies to support the labeled BUD.

### 4.4 Other Tests (Particulates, pH, Visual Inspection)

Both 503A and 503B facilities must ensure that CSPs meet requirements for particulate matter, pH, and appearance. E-beam irradiation does not replace these quality tests. For multi-dose or extended-use vials, preservative efficacy testing may also be required.

## 5. 250-Unit Cap and Lot Sizing

### 5.1 Rationale Behind the Cap

USP FAQs state that sterile compounding in 503A pharmacies is manual; as the batch size increases, the risk of contamination also increases, and the probability of detecting contamination via sampling decreases. Therefore, **CSPs requiring sterility testing** have a maximum batch size of **250 units**. The legal analysis notes that the 250-unit limitation was imposed because larger batch sizes increase the risk of contamination; however, some argue that smaller, more frequent batches may also increase the risk of error and contamination.

### 5.2 Why the Cap Should Not Apply to Terminally Sterilized by Radiation CSPs

- **No reliance on sterility testing** – The 250-unit cap is tied to the sample size required for USP <71> sterility testing. When parametric release is used, sterility assurance is derived from dose validation and process control, rather than sampling. Thus, the statistical rationale underlying the 250-unit limit is irrelevant.
- **Superior SAL** – E-Beam sterilization validated to SAL $10^{-6}$ provides a greater margin of safety than aseptic filtration or steam sterilization (typically SAL $10^{-4}$). The analysis argues that it is inappropriate to apply the same batch size limit to irradiation and moist-heat processes.
- **Risk-based lot sizing** – ISO 11137 allows manufacturers to define lot sizes based on process capability and to perform routine dose audits, with no 250-unit limit. For 503A pharmacies using validated E-Beam sterilization, the lot size should be based on equipment capacity and quality system controls, rather than arbitrary sampling numbers.
- **503B not subject to cap** – Outsourcing facilities already produce large batches under CGMP; applying a 250-unit limit would conflict with federal law and impede patient access to sterile drugs.

## 6. Technology Clause and Allowance for Terminal E-Beam Sterilization

USP <797> permits the use of technologies not explicitly described in the chapter if they are validated and do not bypass safety requirements. The USP FAQs explain that the introduction and scope section allows for technologies, techniques, materials, and procedures not specifically covered, as it would be impossible to address all current and future technologies. The key conditions are that the technology is used according to the manufacturer's approval documentation or, if used for a different purpose, it must be **validated for that purpose** and must not bypass any safety requirements. USP chapters <1223> and <1225> can assist in this validation. The Compounding Expert Committee states that it may develop future guidance. Still, it emphasizes that technologies not covered by <797> may be used as long as they are validated and meet or exceed the chapter's requirements.

This "technology clause" provides a regulatory pathway for adopting **terminal E-Beam sterilization and dosimetric release**. By demonstrating that the process achieves the intended SAL, is validated in accordance with ISO 11137, and is monitored through dose audits, a 503A pharmacy can justify replacing USP <71> sterility testing. Because this approach does not bypass safety requirements and, in fact, provides a higher SAL, it satisfies the technology clause.

## 7. Comparative Discussion: E-Beam Terminal Sterilization vs. Aseptic Filtration

| Parameter | E-Beam Terminal Sterilization | Aseptic Filtration |
|---|---|---|
| Sterility assurance | Validated to SAL $\leq 10^{-6}$; sterility derives from lethal irradiation dose and process validation | Typically, SAL $10^{-3}$–$10^{-4}$; sterility depends on maintenance of aseptic conditions during compounding |
| Process controls | Dosimetry, routine bioburden testing, dose audits and equipment calibration; parametric release based on dose | Media-fill tests, environmental monitoring, filter integrity tests; sterility testing required for extended BUDs |
| Batch size flexibility (503A only) | Batch size limited only by equipment capacity and validated load patterns; no 250-unit cap | Batch size limited by sterility-test sampling requirements (250 units) and manual compounding capacity |
| Time to release | Immediate (after processing) – eliminates 14-day sterility test | Minimum 14 days to complete sterility test |
| Impact on product | Non-thermal; suitable for heat-sensitive CSPs, solid forms and viscous products; must assess potential radiation-induced degradation (potency testing) | Suitable for solutions that can be filtered; not for suspensions or emulsions; risk of post-filtration contamination |
| Regulatory pathway | Supported by ISO 11137/11737, USP <71> (recognition of limitations), USP technology clause and FDA guidance on parametric release; requires documentation and validation | Established under USP <797> and <71>; widely accepted but offers lower SAL and less efficient release |

E-Beam processing, therefore, offers a **superior sterility assurance**, faster release, and scalability. Its primary limitations are the requirement for specialized equipment, the need to validate dose and assess potential chemical degradation (potency testing), and regulatory acceptance by state Boards.

## 8. Anticipated Regulatory Challenges and Counter-Arguments

- **Challenge: USP <71> and state regulations require sterility testing; eliminating it may violate the standards.**

**Response:** USP <71> explicitly states that sterility tests alone do not assure product sterility and that sterility assurance must come from process validation. ISO 11737-2 notes that sterility tests on fully sterilized products provide no valid data and are not recommended. FDA's parametric release guidance allows release without sterility testing when sterilization processes are validated and controlled. The technology clause in USP <797> permits the use of alternative technologies if they are validated and not inferior in quality. Thus, regulatory bodies have already acknowledged that validated terminal sterilization may be released without USP <71> tests.

- **Challenge: Applicability of 250-unit cap to 503A only.**

**Response:** The 250-unit cap is tied explicitly to CSPs requiring sterility testing; the USP FAQs justify it based on the decreasing probability of detecting contamination with increased batch size. Since parametric release does not rely on sampling, the statistical basis for the cap does not apply. Medizap notes that imposing a 250-unit cap on terminally sterilized CSPs ignores the higher SAL of irradiation and imposes unnecessary burdens. Therefore, the cap does not apply to validated E-Beam terminal sterilization processes.

- **Challenge: Endotoxin and potency testing obligations remain.**

**Response:** E-beam sterilization does not remove endotoxins; USP <85> endotoxin testing is still required for CSPs. Potency testing via validated methods (e.g., HPLC) should be conducted to ensure that irradiation does not degrade the API. The dosimetric release argument only addresses sterility testing; it does not replace other quality tests.

- **Challenge: Radiation may degrade sensitive drugs.**

**Response:** Before adopting E-Beam sterilization, a stability study should be conducted to assess drug potency, degradation products, and excipient compatibility. The majority of sterile compounds can tolerate radiation doses when properly formulated. If stability data show unacceptable degradation, E-Beam sterilization should not be used.

- **Challenge: Equipment cost and expertise.**

**Response:** E-beam facilities require significant capital investment and technical expertise. 503A pharmacies may partner with contract sterilizers that operate under ISO 11137 and provide validated dose audits. Documentation from the contract sterilizer should be incorporated into the pharmacy's quality system.

## 9. Final Conclusions and Regulatory Recommendations

1. **State Boards of Pharmacy and FDA should recognize validated E-beam terminal sterilization with dosimetric release as a compliant alternative to USP <71> sterility testing for CSPs prepared by 503A pharmacies and 503B outsourcing facilities.** This position is supported by ISO 11737-2's statement that sterility testing provides no scientific value for fully sterilized products, USP <71>'s acknowledgement that sterility tests do not ensure batch sterility, and FDA guidance on parametric release.
2. **Dosimetric release must be underpinned by rigorous validation and ongoing control**. Pharmacies must establish the sterilization dose using ISO 11137 methods, perform routine dose audits at least every three months or according to a risk-based rationale that considers bioburden, microorganism resistance, and process controls, and monitor each batch using dosimeters.
3. **Endotoxin testing (USP <85>), Potency testing (HPLC or equivalent), and other quality tests remain mandatory**. Terminal sterilization does not remove endotoxins or obviate the need for potency and stability assessments. 503A and 503B entities should continue to perform these tests in accordance with USP and CGMP; only the sterility test is replaced by parametric release.
4. **The 250-unit batch-size cap should not apply to terminally sterilized CSPs released by dosimetry.** Since sterility assurance derives from process validation rather than sampling, the statistical rationale for the cap is not relevant. State Boards should allow larger lot sizes when validated E-Beam sterilization is used.

5. **USP <797>'s technology clause provides a legal basis for adopting terminal E-beam sterilization**. The chapter permits alternative technologies when they are validated and not inferior. USP FAQs confirm that technologies not covered by the chapter may be used if they are validated and do not bypass safety requirements.
6. **Regulatory agencies should issue guidance acknowledging the use of parametric release for compounded sterile preparations**. Clear FDA and state guidance would encourage adoption of higher-assurance sterilization technologies, reduce unnecessary sterility testing, and facilitate access to sterile compounded drugs while maintaining patient safety.
7. By integrating ISO 11137/11737 standards, USP guidance, and FDA precedent, this analysis demonstrates that **terminal E-Beam sterilization with dosimetric release is a scientifically sound, regulatory-compliant, and superior alternative to traditional sterility testing**. Adoption of this approach will enhance sterility assurance, permit reasonable batch sizes, and streamline compounding operations while preserving necessary quality controls such as endotoxin testing and potency assays as required.