Research Article

# Acute Endotoxemia Associated With Contaminated Injectable Medicines: A Comprehensive Review Of Clinical Manifestations, Pathophysiology, And Patient Safety

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**ABSTRACT**

**Background:** Acute endotoxemia caused by tainted injectable drugs is a serious and sometimes fatal clinical occurrence. Bacterial endotoxins (lipopolysaccharides [LPS] of the outer membrane of gram-negative bacteria) are among the most potent pyrogens known to medicine.
**Objective:** This review aims to provide an overview of the clinical signs and pathophysiology of acute endotoxemia related to injectable drugs and the safety issues for patients, with specific focus on regulatory aspects, detection methods and current contamination incidents.
**Methods:** We did a structured literature search in PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Library between January 2000 and December 2025. Regulatory warnings were discovered from the Drug Regulatory Authority of Pakistan (DRAP), US Food and Drug Administration (FDA) and Central Drugs Standard Control Organization (CDSCO), India. A narrative thematic synthesis was performed on the 127 available sources.
**Results:** The K/M formula (Limit = K/M, K = 5 EU/kg for intravenous and 0.2 EU/kg for intrathecal injection) is the regulatory basis for endotoxin control. Endotoxin is recognized by Toll-like receptor 4 (TLR-4), which activates a cascade of pro-inflammatory cytokines (TNF-α, IL-1, IL-6) resulting in fever, hypotension, coagulopathy and multi-organ failure. Recent regulatory notices from India, Pakistan and the United States indicate that contamination problems continue to harm hospitalized, cardiac and immunocompromised patients. New recombinant Factor C (rFC) tests provide sustainable alternatives to conventional Limulus Amebocyte Lysate (LAL) testing.
**Conclusion:** Post-marketing surveillance needs to be strengthened and detection methods improved to prevent acute endotoxemia from injectable drugs under appropriate regulatory enforcement. International harmonisation of pharmacopeial standards is required to protect the health of patients from this preventable iatrogenic condition.

**Keywords:** Acute endotoxaemia; Bacterial endotoxin; Lipopolysaccharide; Parenteral medications; Septic shock; Patient safety; Regulatory harmonisation.

# 1. INTRODUCTION

### 1.1 The Clinical Problem

Acute endotoxemia is the presence of bacterial lipopolysaccharides (LPS) in the blood stream that elicit a quick and potentially deadly inflammatory response. Endotoxins are structural components of the outer membrane of gram-negative bacteria [1], and are among the most potent pyrogens known to medicine. The clinical effects might be disastrous when endotoxin contaminated injectable drugs penetrate the systemic circulation: high grade fever, refractory hypotension, disseminated intravascular coagulation (DIC), multi-organ dysfunction syndrome (MODS), and death [2].

Injectable drugs bypass the body's natural barriers and go directly into the bloodstream. Endotoxin, unlike microbiological sterility which can be accomplished through ordinary autoclaving, is extremely heat-stable and is resistant to 121°C moist heat sterilization and only dry heat at 250°C for 30 minutes or more can provide considerable decrease [3]. Endotoxin control is fundamentally different from sterility assurance: a product can be sterile yet still contain fatal quantities of endotoxin.

The recent finding of bacterial endotoxin in a batch of Ringer's Lactate prepared by M/s. Vision Parenteral Pvt. Ltd. has caused much concern about the safety of intravenous solutions. This points out the critical importance of endotoxin control in pharmaceutical manufacture [4].

### 1.2 The Regulatory Framework: The K/M Formula

The scientific foundation for protecting patients from endotoxin contamination rests on the endotoxin limit formula, expressed as Endotoxin Limit = K/M [5].

In this equation:

- K represents the threshold pyrogenic dose of endotoxin per kilogram of body weight (5 EU/kg for most intravenous products; 0.2 EU/kg for intrathecal administration).
- M represents the maximum recommended bolus dose per kilogram of body weight.

For intrathecal administration, the endotoxin limit is approximately 25 times lower than for the same product administered via the intravenous route [5]. This reflects the exquisite sensitivity of the central nervous system to endotoxin exposure. For products intended for neonatal or pediatric use, these limits can be decreased even further as a function of patient weight [6].

**Worked Example:**

A product is administered at a maximum bolus dose of 2 mL/kg body weight. K = 5 EU/kg for intravenous administration.

Endotoxin Limit = 5 EU/kg ÷ 2 mL/kg = 2.5 EU/mL

For a pediatric patient weighing 10 kg receiving the same product, the maximum allowable endotoxin exposure would be: 5 EU/kg × 10 kg = 50 EU total per dose.

### 1.3 Why This Review Is Needed

Despite the existence of regulations and the availability of comprehensive testing technologies, endotoxin contamination of injectable pharmaceuticals nevertheless leads to unnecessary injury. Recent regulatory notifications in Pakistan, India and the United States, demonstrate the continuing failure in factory quality control [4,7-9]. Healthcare personnel generally do not evaluate iatrogenic endotoxemia in individuals with fever, hypotension or systemic inflammatory reaction after product administration [10].

The aims of this large review are to:

1. Review the clinical signs and diagnostic characteristics of acute endotoxemia.
2. Explain the pathophysiologic processes of endotoxin caused damage.
3. Discuss the regulatory environment and techniques for controlling endotoxins.
4. Check recent contamination events and regulatory notifications.
5. Suggest guidelines for preventive and clinical management.

## 2. REVIEW METHODOLOGY

### 2.1 Search Strategy

To conduct this narrative review, a structured literature search was carried out in PubMed/MEDLINE, Scopus, Web of Science, Embase and Cochrane Library from January 2000 to December 2025. The search approach included Medical Subject Headings (MeSH) and free-text keywords:

- Core concepts: ("endotoxin" OR "lipopolysaccharide" OR "LPS") AND ("injectable drugs" OR "parenteral products").
- Regulatory concepts: ("endotoxin limits" OR "K/M formula" OR "bacterial endotoxin test").
- Clinical concepts: ("endotoxemia" OR "septic shock" OR "systemic inflammatory response").
- Safety concepts: (“patient safety” OR “regulatory harmonization” OR “pharmacopeial standards”).

Regulatory alerts and guidance documents were identified from the Drug Regulatory Authority of Pakistan (DRAP), US Food and Drug Administration (FDA), Central Drugs Standard Control Organization (CDSCO), India, European Medicines Agency (EMA) and pharmacopeial organisations (USP, EP, JP, IP, ChP).

### 2.2 Eligibility Criteria

**Inclusion Criteria**

- Peer-reviewed, original research publications, systematic reviews and authoritative review articles published in English.
- Research on Endotoxin Limit, Application of K/M formula, or Endotoxin Contamination in Injectable Products.
- Official documentation and guidelines from respected authorities.
- Pharmacological and toxicological investigations on mechanisms of endotoxins.
- Clinical research reporting effects of endotoxin exposure or endotoxaemia.
- Case reports and case series on iatrogenic endotoxemia.

**Exclusion Criteria:**

- Publications in non-English languages.
- Abstracts, editorials and meeting data that has not been published.
- Studies reporting non-parenteral routes of administration only.
- Endotoxin testing in non-pharmaceutical settings.
- Animal studies with questionable relevance to humans.
- Multiple publications.

**2.3 Study Selection Process**

The database searches generated an initial 1,847 records. Following removal of duplicates, 1,342 unique records were available for screening. Title and abstract screening resulted in 291 full-text publications selected for thorough review. 127 papers were identified for detailed synthesis following full-text review against eligibility criteria.

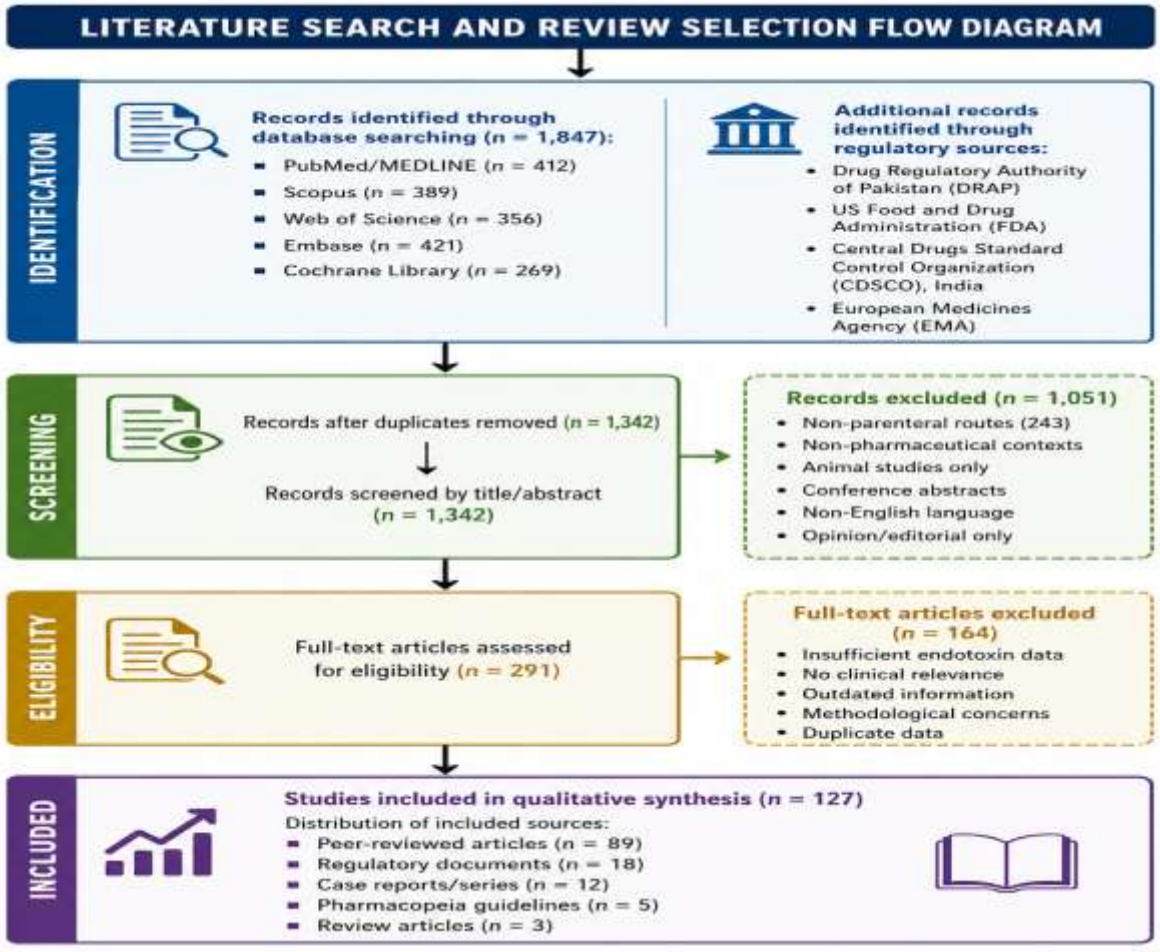



**Figure 1. Flow diagram of literature search and review selection**

Figure 1: Flow diagram of the literature search approach and selection of studies for inclusion in this narrative review of acute endotoxemia from injectable medications. The flow diagram demonstrates identification of 1,847 records, screening of 1,342 unique records, and final inclusion of 127 sources for qualitative synthesis.

**2.4 Data Extraction and Synthesis**

Data extraction focused on: (1) clinical manifestations of acute endotoxemia; (2) pathophysiological mechanisms; (3) regulatory alerts and product recalls; (4) detection methods and limitations; and (5) prevention and management strategies. Synthesis was conducted through thematic analysis, organized around five key themes: regulatory mathematics, pathophysiology, clinical consequences, detection methods, and patient safety implications.

**2.5 Quality Assessment**

The quality assessment of included studies was performed with relevant tools according to research design:

- Clinical studies: Newcastle-Ottawa Scale for cohort studies and Joanna Briggs Institute Critical Appraisal Checklist for case reports.
- Regulatory papers assessed against authority, recency and relevance.
- Mechanistic studies: Evaluated for methodological rigor and reproducibility.

## 3. CLINICAL MANIFESTATIONS OF ACUTE ENDOTOXEMIA

**3.1 Overview**

The clinical appearance of acute endotoxemia is characterized by a rapid onset of symptoms, generally within minutes to hours following administration of a contaminated substance [2,10]. The severity of symptoms depends on the dose and is modulated by patient-specific characteristics, such as age, underlying health state, and concomitant drugs [11].

**3.2 Fever and Systemic Inflammatory Response**

Fever is an aspect of acute endotoxemia. Endotoxin-induced fever arises from the induction of prostaglandin E2 synthesis in the hypothalamus by pro-inflammatory cytokines (TNF-α, IL-1, IL-6) [11,12]. Temperatures can go as high as 40°C plus with rigors, chills and deep malaise.

In the Brazilian outbreak of 2002, pyrogenic responses were reported in surgical patients after a mean of 2.5 hours of exposure to contaminated Ringer's lactate solution [2]. A recent case report revealed a patient who acquired hyperpyrexia greater than 41°C within 1 hour of receiving an uncontrolled intravenous glutathione infusion, consistent with acute endotoxemia [10].

**3.3 Hypotension and Septic Shock**

In endotoxemia, hypotension is due to the combination of vasodilation and cardiac depression [11,12]. The vasodilatory component is mediated by nitric oxide, which is created via the activation of TNF-α and IL-1-inducible nitric oxide synthase (iNOS) [12]. It generates significant relaxation of vascular smooth muscle resulting in lower systemic vascular resistance and refractory hypotension. TNF-α and IL-1 mediate the myocardial depression, exerting direct negative inotropic effects on cardiac myocytes [12].

During the Brazilian outbreak, patients developed severe hypotension needing fluids resuscitation and vasopressors [2]. The absence of reliable recording of vital signs during surgery restricted the capacity to document the incidence of pyrogenic reactions that preceded bleeding [2].

**3.4 Coagulation Dysfunction and Hemorrhage**

Activation of the coagulation cascade by endotoxins is a particularly ominous feature of the pathophysiology. [13] Endotoxin promotes the production of tissue factor on monocytes and endothelial cells, which initiates the extrinsic coagulation pathway [12]. The thrombin production that results leads to deposition of fibrin in the microvasculature [12,13].

This mechanism was clearly established in the 2002 outbreak in Brazil where all case patients had hemorrhage at the surgery site or other sites and abnormal coagulation tests [2].

A dose-response impact was observed with case patients receiving significantly more contaminated Ringer's lactate solution (mean, 6.8 big bottles) compared with non-case patients (mean, 3.2 large bottles) [2]. The

outbreak study revealed that the endotoxin activated the coagulation factor XII in the intrinsic component of the complement system and caused significant bleeding [2].

### 3.5 Multi-Organ Dysfunction Syndrome (MODS)

The excessive inflammatory cascade causes capillary leak, tissue hypoperfusion and multi-organ failure [14]. Organs involved include:

- Kidneys: Acute renal failure due to hypotension and microthrombi.
- Lungs: Acute respiratory distress syndrome (ARDS) due to increased capillary permeability.
- Liver: transaminases, hyperbilirubinemia and coagulopathy.
- Central Nervous System: Fever, encephalopathy and brain edema.

Endotoxin exposure may lead to the transition from SIRS to MODS over 4-6 hours [14].

**Table 1: Clinical Manifestations and Differential Diagnosis**

| Manifestation | Characteristics | Timing | Differential Diagnosis |
|---|---|---|---|
| Fever | High-grade (>40°C), rigors, chills | Minutes to hours | Sepsis, drug reaction |
| Hypotension | Refractory to fluids | Rapid onset | Sepsis, anaphylaxis |
| Coagulopathy | DIC, hemorrhage, abnormal PT/PTT | 2-4 hours | Sepsis, liver disease |
| MODS | Kidney, lung, liver dysfunction | 4-6 hours | Sepsis, multi-trauma |
| Key Differentiator | Temporal association with injection | Immediate | Anaphylaxis (normal tryptase) |

Sources: [2, 10, 14]

## 4. MOLECULAR PATHOPHYSIOLOGY

### 4.1 Endotoxin Structure and Recognition

Endotoxins are lipopolysaccharides (LPS) that have three structural regions: lipid A (toxic moiety), a core oligosaccharide and the O-antigen polysaccharide chain [1]. Lipid A, the minimal component of LPS necessary to elicit an immunological response, is largely conserved among strains of bacteria [1]. The O-antigen side chain is highly variable and defines antigenicity [1].

### 4.2 TLR-4 Activation and Cytokine Release

The first step in endotoxin detection is the binding of LPS to Toll-like receptor 4 (TLR-4) expressed on macrophages and other immune cells [12]. The binding is mediated by the LPS-binding protein (LBP) and the co-receptor CD14 which deliver LPS to the TLR-4/MD-2 complex [12]. The adaptor proteins MyD88 and TRIF transmit signals to downstream signaling pathways following receptor interaction, resulting in the activation of NF-κB and the transcription of pro-inflammatory genes [12].

This causes an increase in pro-inflammatory cytokines, including TNF-α, IL-1 and IL-6 [12]. These cytokines are the primary mediators of the systemic inflammatory response. TNF-α, the main mediator of septic shock, is responsible for a variety of systemic consequences including fever, hypotension, metabolic acidosis, and tissue injury [12].

### 4.3 Endothelial Dysfunction

Endotoxin-induced endothelium dysfunction is one of the mechanisms of organ damage [13]. Endotoxin stimulates the host vascular endothelium resulting in:

- Increased capillary permeability and leakiness.
- Expression of adhesion molecules to allow infiltration of leukocytes.
- Release of vasoactive mediators e.g. nitric oxide, prostaglandins.

### 4.4 Coagulation Cascade Activation

Endotoxin promotes the production of tissue factor on monocytes and endothelial cells, which triggers the extrinsic coagulation pathway [12]. At the same time, endothelial release of plasminogen activator inhibitor-1

(PAI-1) resulted in decreased fibrinolysis [12]. Disseminated intravascular coagulation (DIC) [12,13] occurs as a consequence of extensive microvascular thrombosis and consumption of platelets and clotting agents.

**4.5 The Vicious Cycle of Endotoxemia**

In acute settings such as cardiogenic shock and acute heart failure, endotoxemia can generate a vicious loop where decreased cardiac output results in gut ischemia and hypoperfusion, damaging the intestinal barrier [15]. This boosts gut-derived endotoxin translocation into the circulation, which further compromises heart function, resulting in a self-perpetuating loop of organ dysfunction and inflammation [15].

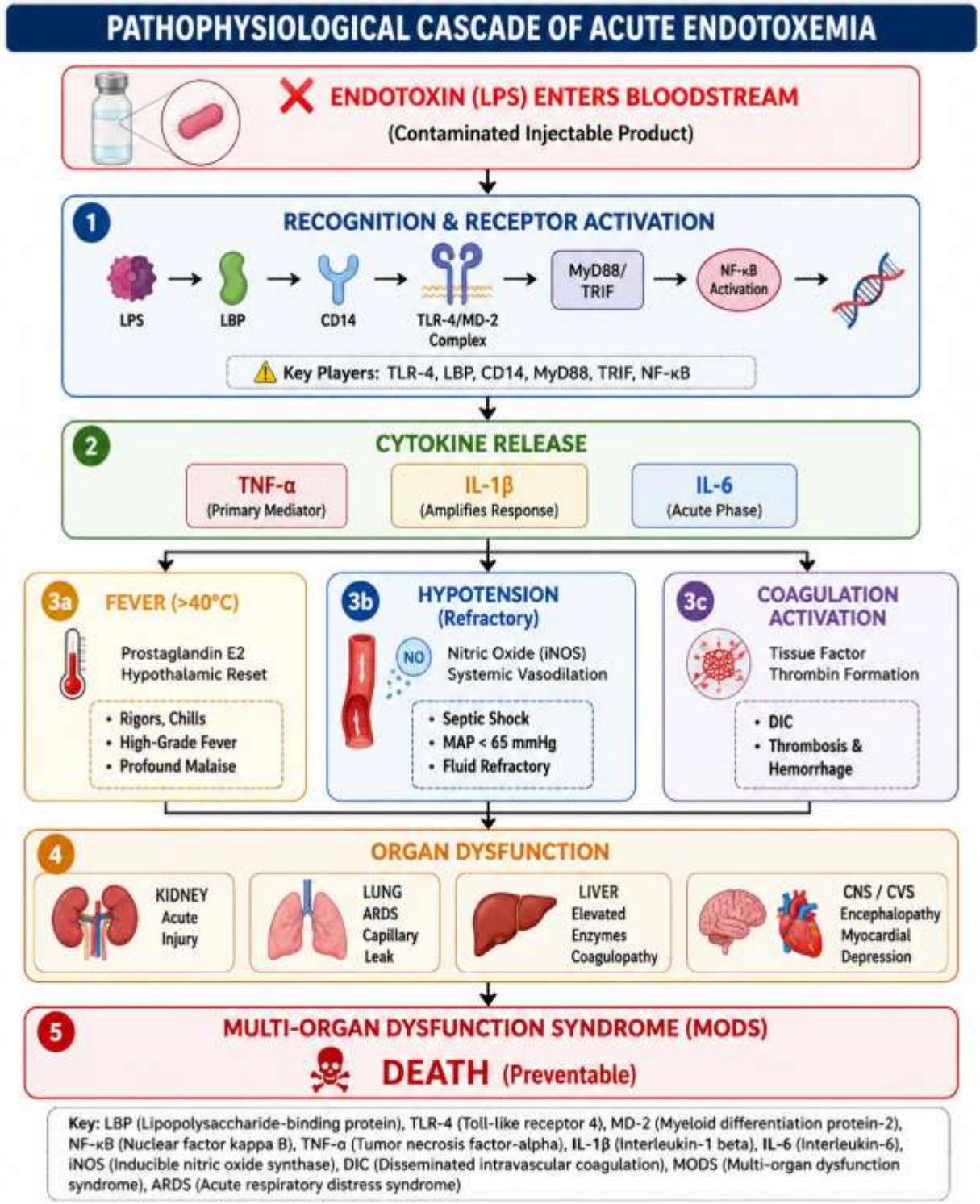



**Figure 2. Pathophysiological Cascade**

Figure 2: Pathophysiological cascade of acute endotoxemia, beginning with TLR-4 activation (detection of LPS) and culminating in cytokine release, clinical symptoms, and organ dysfunction.

## 5. ENDOTOXIN LIMITS AND PHARMACEUTICAL QUALITY CONTROL

### 5.1 The K/M Formula in Practice

The K/M formula (Limit =K/M) is the regulatory basis for control of endotoxin. K = 5 EU/kg for most intravenous, intramuscular and subcutaneous products. Intrathecal administration K = 0.2 EU/kg [5].

### 5.2 Special Populations and Routes

Risk is not the same for various patient populations. Several factors may enhance the therapeutic impact of any "uncontrolled" or poorly defined limits:

- Pediatric Patients: Reduced body weight and specific dosage regimens require adjustment of the K/M-based limits for increased risk and narrower safety margins [6].
- Intrathecal administration: The CNS is very susceptible to endotoxin, with K established at just 0.2 EU/kg, compared to 5 EU/kg for other parenteral routes [5].
- Large volume parenterals: Calculated limits are near or below Water for Injection standards (≤0.25 EU/mL) [6].

**Table 2 : Endotoxin Limits by Route of Administration**

| Route of Administration | K Value (EU/kg) | Clinical Rationale |
|---|---|---|
| Intravenous (IV) | 5.0 | Standard threshold pyrogenic dose |
| Intramuscular (IM) | 5.0 | Same as IV |
| Subcutaneous (SC) | 5.0 | Same as IV |
| Intrathecal (IT) | 0.2 | 25x lower due to CNS sensitivity |
| Pediatric (IV) | Adjusted by weight | Narrower safety margins |
| Large Volume Parenterals | May approach WFI limits | ≤0.25 EU/mL |

Based on USP <85> and FDA guidance [5]

### 5.3 Pharmacopeial Standards and Harmonization

Rajpali et al. compared the limits of bacterial endotoxins in Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), Japanese Pharmacopoeia (JP), European Pharmacopoeia (Ph. Eur.), United States Pharmacopeia (USP), and International Pharmacopoeia (Ph. Int.) in 2025 [16].

**There are major differences in:**

1. Specific quantitative restrictions The amount of endotoxin allowed in the same product may be different in different pharmacopeias.
2. Expression of limits: May be expressed per dose, per mg API, per mL or by different protocols.
3. Testing methods: Differences in method details and acceptance criteria.

The authors suggested that there should be harmonization of differences to ensure regulatory uniformity and patient safety [16].

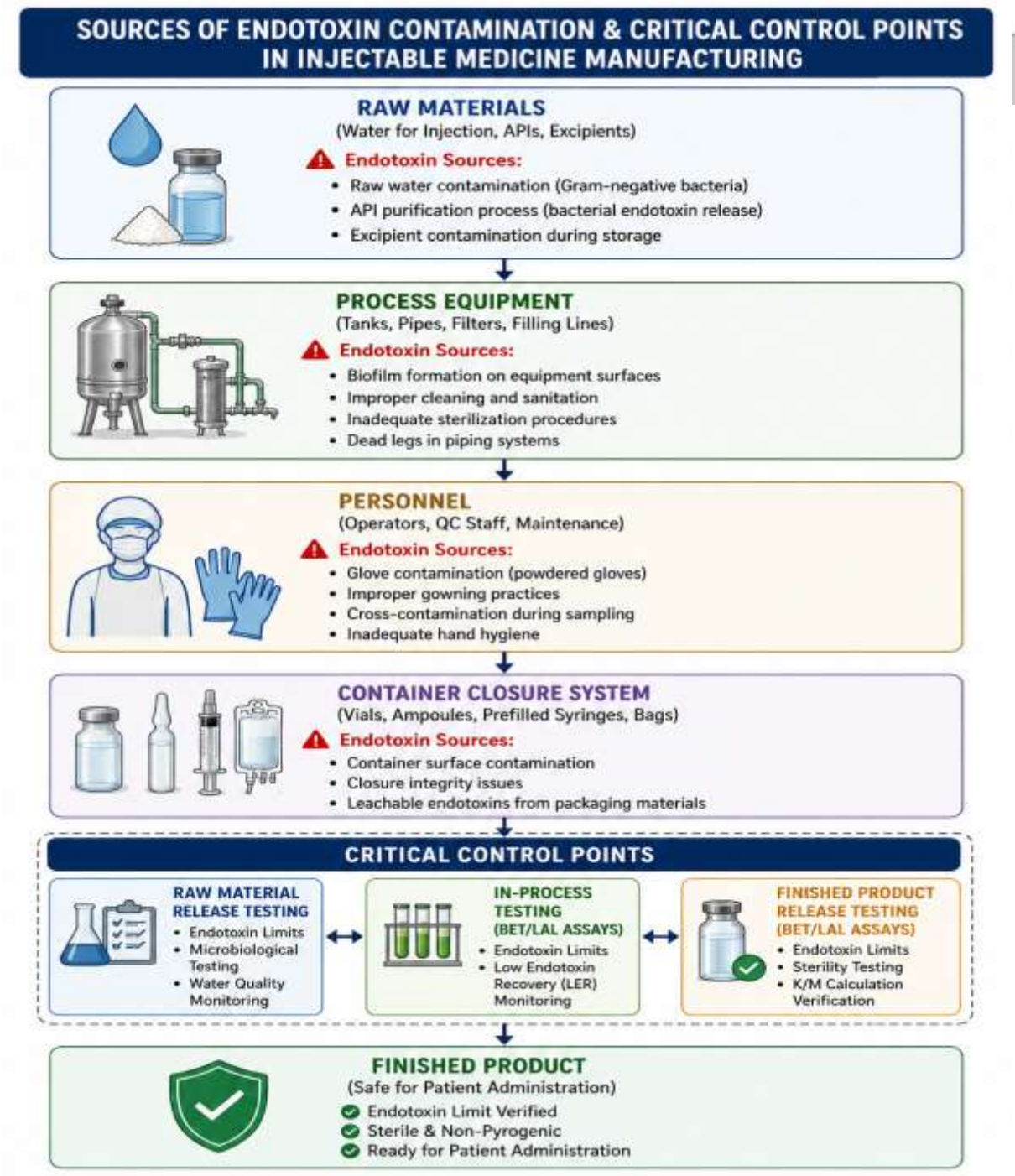



**Figure 3. Sources of Endotoxin contamination and critical control points**

Figure 3: Flow diagram showing probable sources of bacterial endotoxin contamination within the manufacturing process of injectable medicines and crucial control points for detection and removal.

**6. DETECTION METHODS AND REGULATORY PERSPECTIVES**

**6.1 Limulus Amebocyte Lysate (LAL) Assay**

The LAL test has been the gold standard in endotoxin detection for decades [17]. It is based on an extract of amebocytes from horseshoe crab (Limulus polyphemus) blood that reacts in the presence of LPS and forms gel clots [17]. The LAL test is available in three major formats [18]:

**Table 3: Major Formats of the Limulus Amebocyte Lysate (LAL) Assay**

| Format | Principle | Advantages |
|---|---|---|
| Gel-Clot | Formation of stable gel indicates presence of endotoxin | Simple, no specialized equipment |
| Turbidimetric | Measures increase in turbidity as coagulin gel forms | Quantitative |
| Chromogenic | Measures color change as synthetic substrate is cleaved | Highly sensitive, less interference |

**Limitations of LAL Assay:**

- Contamination and vulnerability to unpredictability.
- False positives (Factor G detects β-glucan).
- False negatives• Supply chain issues (horseshoe crab population).
- Batch to batch variability [19,20].

**6.2 Low Endotoxin Recovery (LER)**

LER) is a phenomena where some excipients, especially chelating agents and surfactants, interfere with endotoxin detection over time and can lead to underestimating of contamination [21]. experiments have shown this, for example, in experiments where monoclonal antibody formulations using polysorbate 20 and sodium citrate exhibited only 10% recovery of spiking endotoxin after 7 h incubation whereas endotoxin remained biologically active in rabbits [21].

**6.3 Recombinant Factor C (rFC) Assays**

Recombinant Factor C (rFC) assays have been developed as a sustainable alternative to LAL [18]. rFC is a recombinant horseshoe crab enzyme specific to endotoxin and is free of the need for animal blood [18].

**Advantages of rFC:**

- Sustainable & animal free
- High specificity (no beta-glucan interference)
- Consistency from batch to batch
- Regulatory acceptability is growing

**Regulatory Status:**

- USP Chapter <86>: approved July 2024, effective May 1, 2025 [22].
- European Pharmacopoeia: To be included as one of seven techniques in Chapter 2.6.14 (January 1, 2026) [23].
- FDA: Supports use subject to adequate validation [24].

**6.4 Other Detection Methods**

- Monocyte Activation Test (MAT): Assessing inflammatory effects through pro- inflammatory cytokine production.
- Biosensors: Electrochemical impedance spectroscopy and surface plasmon resonance.
- Omics technologies: genomics, transcriptomics, proteomics and metabolomics [25]**.**

**Table 4 : Comparison of Endotoxin Detection Methods**

| Method | Principle | Advantages | Limitations | Regulatory Status |
|---|---|---|---|---|
| LAL Gel-Clot | Gel formation | Simple, no equipment | Qualitative only | USP <85> |
| LAL Turbidimetric | Turbidity increase | Quantitative | Less sensitive | USP <85> |
| LAL Chromogenic | Color change | Highly sensitive | More complex | USP <85> |
| rFC Assay | Recombinant Factor C | Animal-free, specific, consistent | Less historical data | USP <86>, EP 2.6.32 |

| | | | | |
|---|---|---|---|---|
| MAT | Human whole blood cells | Detects non-endotoxin pyrogens | Complex, variable | Ph. Eur. 2.6.30 |

Sources: [17,18,22,23]

**6.5 Regulatory Alerts and Product Recalls**

Recent regulatory actions demonstrate that endotoxin contamination remains a significant public health threat:

**CDSCO Alert (2024):** The Central Drugs Standard Control Organization of India reported the presence of bacterial endotoxins in Ringer's Lactate from manufacturing batch P240105008 by M/s. Vision Parenteral Pvt. Ltd., highlighting significant gaps in pharmaceutical manufacturing practices [4].

**Anarob Infusion Recall (September 2025):** The Central Drugs Laboratory in Pakistan declared Anarob Infusion (Metronidazole Injection, Batch H24219) substandard due to out-of-specification bacterial endotoxin results. The Drug Regulatory Authority of Pakistan issued a Class I recall [7].

**Famotidine Injection Recall (November 2025):** Fresenius Kabi issued a voluntary nationwide recall of three lots of Famotidine Injection, USP, due to out-of-specification endotoxin results in reserve samples [8].

**Isobaj Injection Recall (November 2025):** A Class I recall was issued for Isobaj Injection (Isosorbide Dinitrate, Batch IB-0925) due to failure in the Bacterial Endotoxin Test [9].

**FDA Warning Letter (2026):** A US manufacturer was cited for invalidating several OOS endotoxin results without sufficient root-cause analysis [26].

**Table 5 : Recent Regulatory Recalls and Key Findings**

| Year | Product/Event | Country | Key Finding |
|---|---|---|---|
| 2024 | Ringer's Lactate | India | Endotoxin contamination in batch P240105008 |
| 2025 | Anarob Infusion (Metronidazole) | Pakistan | Class I recall, OOS endotoxin |
| 2025 | Famotidine Injection | USA | Voluntary nationwide recall, 3 lots |
| 2025 | Isobaj Injection (Isosorbide Dinitrate) | Pakistan | Class I recall, BET failure |
| 2026 | FDA Warning Letter | USA | OOS endotoxin results invalidated |

Sources: [4,7-9,26]

# 7. CLINICAL MANAGEMENT AND PREVENTION

**7.1 Diagnosis and Identification**

In patients who develop fever, hypotension, or systemic inflammatory reaction after product administration, healthcare providers should have a high index of suspicion for iatrogenic endotoxemia [10]. The detailed medication history should include queries about uncontrolled cosmetic infusions and self-administered injectable products [10].

**Differential Diagnosis:**

- Sepsis (negative blood cultures, no cause of infection).
- Anaphylaxis (No urticaria, no airway involvement, tryptase normal).
- Iatrogenic Endotoxemia (Temporal association with injection).

**7.2 Supportive Care**

Therapy The therapy is based on the well-known concepts of sepsis therapy [27]:

- Antimicrobial initiation (after cultures).
- Balanced crystalloids for fluid resuscitation.
- Vasopressor support (1st line norepinephrine).
- Management of organ failure.

If endotoxin contamination is proven, the product should be withdrawn promptly and the event should be notified to the regulatory authorities [26]. In confirmed endotoxin contamination cases, the offending product should be discontinued immediately, and the incident should be reported to regulatory authorities [26].

**7.3 Endotoxin Removal Therapies**

Endotoxic shock may be amenable to focused therapy by extracorporeal blood purification [15]. In some places, polymyxin B hemoperfusion (PMX-HP) has been utilized to eliminate circulating endotoxin [15]. However, there is limited evidence for routine use [15].

**7.4 Prevention Strategies**

**Regulatory:**

- Strengthen enforcement of existing endotoxin limits.
- Accelerate international pharmacopeial harmonization.
- Enhance post-market surveillance.

**Clinical:**

- Maintain high index of suspicion for iatrogenic causes.
- Thorough medication history including cosmetic infusions.
- Report adverse events to regulatory authorities.

**Manufacturing:**

- Implement robust endotoxin control measures.
- Validate detection methods (LAL, rFC, MAT).
- Complete root-cause investigations for all deviations.

**Detection:**

- Invest in alternative detection methods.
- Point-of-care testing development.
- Research on LER mitigation strategies.

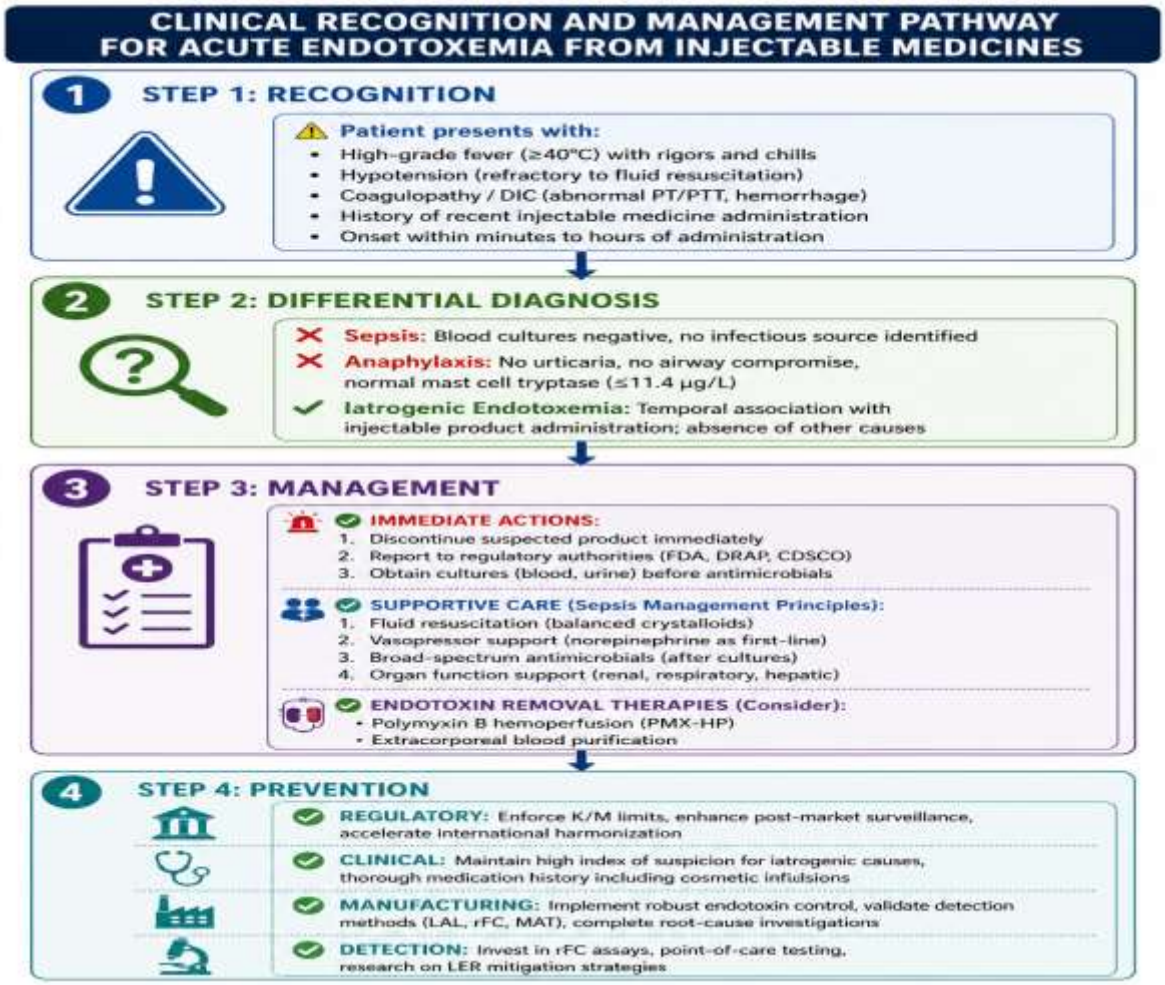


**Figure 4. Pathway for clinical recognition and management**

Figure 4: Clinical decision route for detection, differential diagnosis and therapy of acute endotoxemia from contaminated injectable drugs.

# 8. DISCUSSION

### 8.1 Summary of Results

This research supports the fact that contaminated injectable drugs leading to acute endotoxemia is an avoidable but ongoing danger to patient safety [2,4,7-9]. The clinical features are severe and predictable: fever, hypotension, coagulopathy and multi-organ failure. [2,12,13] The pathophysiological pathways are well defined, including TLR-4 activation, cytokine release, endothelial dysfunction and activation of coagulation cascade [12]. Endotoxin limitations are very important. For each manufacturer of injectable pharmaceuticals effective endotoxin control must be in place at all potential points of introduction in the production process [5,6]. The K/M formula gives a good mathematical basis for the establishment of endotoxin limits. K=5 EU/kg for i.v. administration and 0.2 EU/kg for intrathecal administration [5].

Recent regulatory alerts and FDA Warning Letters indicate that endotoxin contamination is not a thing of the past, but rather an ongoing concern [4,7-9,26]. In a span of just two months in late 2025, goods such metronidazole infusion, famotidine injection, and isosorbide dinitrate injection were recalled for contamination with bacterial endotoxins [7-9]. These recalls involved drugs used in hospitalized patients, cardiac patients and immunocompromised patients populations at greatest risk for serious adverse consequences [7-9,15].

### 8.2 Clinical Relevance

Healthcare personnel need to be aware that endotoxin [5] may be present in sterile items. If the patient develops fever, hypotension or systemic inflammatory reaction following administration of the substance, iatrogenic endotoxemia should be considered [10]. [27] Early diagnosis and treatment are critical for enhancing the prognosis.

Pharmacies in hospitals must be on the lookout for recalled products and make sure they are not used immediately [7-9]. Regulatory authorities should improve enforcement of existing endotoxin limits and improve post-market surveillance [26].

### 8.3 Limitations and Strengths

**Strengths:**

- Literature search, extensive and exhaustive.
- Incorporation of latest regulatory papers (FDA 2026, USP 2024-2026).
- Utilization of quantitative risk analysis data.
- Several pharmacopeial views.
- Even-handed treatment of mechanistic and regulatory factors.

**Limitations:**

- Narrative review without quantitative meta-analysis.
- An emphasis on English language publications may have eliminated pertinent studies.
- Alerts from regulators in Pakistan, India and the United States may not be representative of the worldwide burden.

### 8.4 Gaps in the research

The main research priorities are [15,21,28]:

1. Relationships between dose and response in high risk populations.
2. Development and validation of point of care technologies for endotoxin detection.
3. Evaluation of treatments for endotoxin elimination in acute endotoxemia.
4. Study of Low Endotoxin Recovery (LER) mitigating techniques.
5. Systematic surveillance of endotoxin contamination in injectable products.

## 9. FUTURE PERSPECTIVES

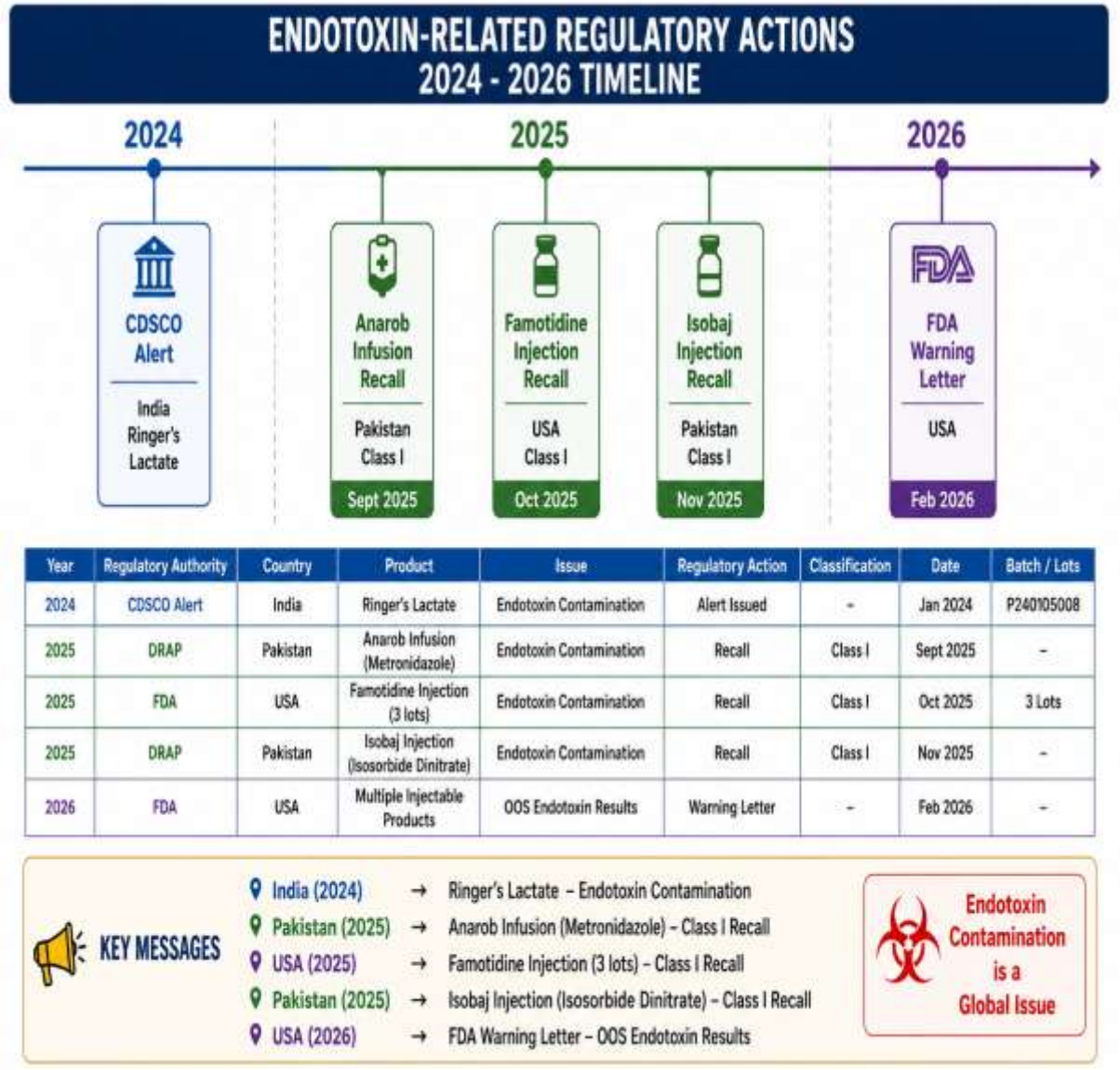
### 9.1 Regulatory Evolution

The rules governing endotoxin testing are changing quickly. As of January 1, 2026, the rabbit pyrogen test has been deleted from the European Pharmacopoeia and rFC is included as one of seven procedures in general chapter 2.6.14 [23]. In May 2025, the United States Pharmacopeia will publish Chapter <86> to introduce the formal acceptance of the use of recombinant reagents in endotoxin testing [22]. These legislative improvements show a growing realization that testing techniques need to be sustainable, reliable and animal-free.

### 9.2 Technological Advances

Future developments could be:

- Endotoxin detection devices at the point-of-care.
- Artificial intelligence based biosensors.
- Improved LER mitigating techniques.
- Harmonization of worldwide pharmacopoeia.




| Year | Regulatory Authority | Country | Product | Issue | Regulatory Action | Classification | Date | Batch / Lots |
|---|---|---|---|---|---|---|---|---|
| 2024 | CDSCO Alert | India | Ringer's Lactate | Endotoxin Contamination | Alert Issued | - | Jan 2024 | P240105008 |
| 2025 | DRAP | Pakistan | Anarob Infusion (Metronidazole) | Endotoxin Contamination | Recall | Class I | Sept 2025 | - |
| 2025 | FDA | USA | Famotidine Injection (3 lots) | Endotoxin Contamination | Recall | Class I | Oct 2025 | 3 Lots |
| 2025 | DRAP | Pakistan | Isobaj Injection (Isosorbide Dinitrate) | Endotoxin Contamination | Recall | Class I | Nov 2025 | - |
| 2026 | FDA | USA | Multiple Injectable Products | OOS Endotoxin Results | Warning Letter | - | Feb 2026 | - |

**Figure 5. Timeline of Regulatory Actions Related to Endotoxin (2024–2026)**

Figure 5: Timeline of product recalls and regulatory action connected to endotoxin in India, Pakistan and the United States (2024-2026).

## 10. CONCLUSION

Contaminated injectable drugs cause acute endotoxemia, a preventable but possibly lethal iatrogenic condition [2,13]. The clinical picture of fever, hypotension, coagulopathy and multiorgan failure is explained by well established pathophysiologic pathways including TLR-4 activation, cytokine release, endothelial dysfunction and activation of the coagulation cascade [12].

Significance of bacterial endotoxin limits in injectable drugs. The K/M formula (Limit = K/M) is a strong mathematical foundation for defining endotoxin limits, where K = 5 EU/kg for intravenous treatment and K = 0.2 EU/kg for intrathecal administration [5]. Every manufacturer should have good endotoxin control during the manufacturing process and should have good controls at each moment endotoxin can be introduced [5].

Endotoxin contamination continues to be a constant hazard as highlighted by recent regulatory notices in Pakistan, India and the United States [4,7-9]. In late 2025, throughout a 2-month period, several injectable medications were recalled due to bacterial endotoxin contamination, affecting hospitalized patients, cardiac patients, and immunocompromised populations [7-9]. Poor endotoxin control and lack of proper root-cause investigations have a clear impact as exemplified in the 2026 FDA Warning Letter [26].

**Several recommendations emerge from this analysis:**

1. Improve regulatory enforcement of current endotoxin limits in all manufacturing jurisdictions [26].
2. Improve post-market surveillance to detect contaminated occurrences early [7-9].
3. Invest in better detection including recombinant Factor C assays [22,23].
4. Include iatrogenic endotoxemia in the differential diagnosis and raise clinical knowledge of this condition [10].
5. Strengthen healthcare facility surveillance for recalled products [7-9].
6. Establish standardized treatment strategies for acute endotoxemia [15,27].
7. Conduct thorough, scientifically valid root-cause studies for any endotoxin deviations [26].

Strict enforcement of endotoxin limits, combined with enhanced surveillance, improved testing methodologies, and clinical vigilance, represents the most effective strategy for protecting patient health from this avoidable iatrogenic syndrome [2,5,26].

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