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ORIGINAL RESEARCH ARTICLE

A Nontrivial Analysis of Patient Safety Risk from Parenteral Drug- and Medical Device-Borne Endotoxin

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Abstract

Background A thorough and systematic analysis of potential endotoxin-related safety issues from parenteral drugs and devices is important to ensure appropriate current Good Manufacturing Practices, compendial requirements, standards and regulatory guidance. Lately, the US Food and Drug Administration has been expecting pharmaceutical firms to apply an arbitrary safety factor to compendial compliant drug specifications for endotoxin, potentially causing manufacturing challenges, supply issues and additional unwarranted costs.

Objective The aim of this study was to evaluate data from three disparate sources over an extended period of time, from 2008 to 2021, to determine if there exists an industry-wide risk to patients from parenteral drugs and devices, thereby evaluating if changes to current Good Manufacturing Practices or compendial requirements are indeed warranted. Food and Drug Administration data from current Good Manufacturing Practices non-compliance observations, product recalls and the FDA Adverse Event Reporting System were used as the three sources of data.

Methods Parenteral products were separated into drugs and devices, potential endotoxin-related patient safety issues were characterised in terms of the available non-compliance information, the type and number of product recalls, and the type and number of potential adverse events. Descriptive statistics in Microsoft Excel 2019 and Pivot tables were used for the analysis and presentation of the data.

Results From 2011 to 2021, a total of 188 endotoxin-related current Good Manufacturing Practices compliance observations were recorded, 70% and 30% were associated with laboratory and manufacturing origins, respectively. Finished drug product testing accounted for 56% of these. In contrast, 95% of all endotoxin-related product recalls were associated solely with medical devices. Over the years 2008–2021, approximately 1.4% of all adverse events (23,663,780) were recorded with some reference to pyrexia (fever); however, there are sparse data categorically attributing this to the administration of parenteral drugs or devices or combinations of these possessing high levels of endotoxin.

Conclusions Analysis of data concerning drug- and device-borne endotoxin obtained from FDA data from current Good Manufacturing Practices non-compliance observations, product recalls and the FDA Adverse Event Reporting System demonstrated the absence of industry-wide issues with endotoxin contamination. Based upon these data, changes to current Good Manufacturing Practices and the compendial methodology of setting endotoxin specifications (and hence the compendial methodology of testing for endotoxins) are unwarranted.

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Key Points

A systematic approach to evaluating patient safety risk from drug- and device-borne endotoxin will assist in the continuance of meaningful compendial requirements and regulations.

Analysis of current Good Manufacturing Practices non-compliance observations, product recalls and potential endotoxin-related adverse events provided an evaluation of patient safety. The analysis revealed that there are no industry-wide risks due to drug- or device-borne endotoxin.

Current modes of endotoxin manufacturing controls, current Good Manufacturing Practices and compendial methodology of setting endotoxin specifications (and hence the compendial methodology of testing for endotoxins) are sufficient to assure patient safety.

1 Introduction

Parenteral products include fluid injections, combinatorial products and implanted medical devices that are injected through the skin delivering a therapy into the vascular system, organs or specific tissues. This route of administration requires the therapy to be sterile and free of levels of bacterial endotoxins that might jeopardise patient safety by eliciting a pyrogenic response [1]. Bacterial endotoxin is an exogenous pyrogen [2] and the most potent molecular component of bacteria [3] known to induce inflammation and a concomitant cytokine-mediated increase in body temperature [4] (generally regarded as fever); thereby representing a potential patient safety risk.

All parenteral drug products and devices, administered by intravenous, intraventricular, intra-arterial, intra-articular, subcutaneous, intramuscular, intrathecal, intracisternal and intraocular routes, must possess an appropriate endotoxin limit specification to achieve marketing authorisation by health authorities. The ICH Q4B Annex 14 [5] provides the framework by which firms establish endotoxin specifications conforming to health authority (such as the US Food and Drug Administration [FDA]) expectations. Endotoxin specifications are established using a methodology detailed within the harmonised compendia, specifically chapter <85> of the US Pharmacopoeia (USP) [6]. If a drug product label or package insert instructs the use of a specific diluent, reconstituting agent or administration vehicle, the contribution of endotoxin from this must also be accounted for during the calculation of the endotoxin specification limit for the finished drug product [7]. All lots of parenteral drug products are released to the market only by successfully completing a test for bacterial endotoxins using an assay conforming to the USP <85> [6]. In the USA, the Code of Federal Regulations (CFR) 21 CFR 211.160 [8] and 21 CFR 211.165 [9] are the statutory regulations requiring parenteral drug products to possess appropriate written specifications, sampling and testing to assure conformance to endotoxin specification limits. Similarly, 21 CFRs 820.70 [10], 21 CFR 820.250 [11] and USP <161> [12] are the equivalent legal and compendial requirements for medical devices. These regulations and standards have assured patient safety for decades through robust endotoxin specifications and testing compliant with compendial requirements.

Notwithstanding the history of parenteral drug and device patient safety, there have been recent reservations expressed by the FDA concerning the adequacy of the compendial method of setting endotoxin limits, specifications and testing for endotoxins. In response to market license applications, the Center for Drug Evaluation and Research has requested firms add an arbitrary 'safety factor' to endotoxin specification limits [13]. Here, the safety factor is an additional numerical denominator of the drug product endotoxin specification; simply arbitrarily halving the specification limit. In this context (sterile products), the issue is purely the presence of endotoxin representing residues of the Gram-negative outer cell membrane and not associated with viable cells. It is possible that safety factors are requested based upon a misperception of assay variability associated with the compendial standard test for endotoxins performed during release testing. Akers et al. [14] have detailed how the compendial method of setting endotoxin limits itself includes an inherent significant safety margin and the attendant scientific explanations accounting for decades of patient safety. Despite this, the question remains 'is there a genuine industry-wide problem with drug- and device-borne endotoxin (or combinations thereof) warranting a change to Good Manufacturing Practices (cGMPs) and the means of establishing endotoxin specifications?'

Until now, there has been limited documented analysis of empirical data objectively evaluating what (if any) patient endotoxin-related safety risk exists from inadequate cGMPs, finished drug product and device endotoxin specifications (or testing). The purpose of this study was to systematically evaluate data from three disparate database sources and establish a conclusion. These data sources are briefly introduced below:

1. FDA Form 483s: to assure conformance to the CFRs, the FDA performs periodic inspections of parenteral drug and medical device manufacturers under the instrument of the Federal Food, Drug and Cosmetic Act Sec.

704 (21 USC §374) "Factory Inspection" [15]. Upon completion of the inspection, the FDA may issue Form FDA 483, which documents any non-conformance to the requisite regulations, essentially current cGMPs. These Form FDA 483 details are publicly available and provide a useful means of determining where violations to cGMPs may result in potential or developing areas of concern including endotoxin control, specifications and testing in parenteral manufacture.

2. FDA Recalls: where a marketed drug or medical device is considered to be in violation of the laws which the FDA administers, a recall of the items from the market occurs. All FDA-regulated product recalls are curated and their details available from the FDA enforcement website [16]. These data list and detail those products that have been recalled based upon a patient safety risk including risks associated with endotoxins. Accordingly, they provide a second useful means of determining where there could be potential or developing areas of industry-wide concern in endotoxin control, specifications and testing in parenteral manufacture.
3. FDA Adverse Event Reporting System (FAERS): to continuously assess safety concerns related to marketed drug products and medical devices, the FDA maintains the FAERS [17]. Adverse events (AEs) are harmful outcomes when a patient receives medical care [18] inclusive of a procedure, surgery or administration of a therapy causing side effects, injury, psychological harm, trauma or death [19]. Adverse events are not uncommon occurrences with at least one in ten patients affected [20]; in the USA, over 250,000 patients will experience an AE per annum [21].

   The FAERS is a publicly accessible database that contains AE reports, medication error reports and product quality complaints that have been submitted to the FDA. The FAERS represents a comprehensive source of interrogatable data to evaluate patient safety risks. The FAERS curates all reported AEs, which include patient fevers attributable to a range of causes that potentially include drug- and medical device-borne pyrogens/bacterial endotoxins. It is essential to recognise that there exist numerous aetiologies for fever after administration of a parenteral drug. Fever is a consequence of inflammation that may occur because of a malignancy, autoimmune disease, seizure, hyperthyroidism and myocardial infarction amongst other conditions [22]. Voluntary reports are submitted to the FDA by healthcare professionals (e.g. physicians, pharmacists, nurses), consumers (e.g. patients, family members, lawyers) and manufacturers and curated in the FAERS. If a drug or medical device manufacturer receives a report from a healthcare professional or consumer, they are required by statutory regulations 21 CFR 310.305 [23], 314.80 [24], 314.98 [25], 600.80 [26] and 600.81 [27] to submit the report to the FDA. The FAERS provides a third useful instrument determining where there could be potential or developing areas of concern in endotoxin control, specifications and testing in parenteral manufacture.

2 Methods

2.1 Form FDA 483 Database and Datasets

Form FDA 483 data were obtained from Redica Systems [28]. Redica Systems is a quality regulatory intelligence platform that provides cloud-based data intelligence. The platform uses proprietary data sourcing and machine learning models, combined with purpose-built visualisations, for subscribing users to gain immediate access to actionable high-quality data analytics. Redica Systems data include information detailing the site of FDA inspection, country, FDA Center involved in the inspection, project area, inspectors, inspection date, FDA listed issues and associated keywords, and the observation text recorded in each Form FDA 483. The observation text provides significant details concerning each cGMP violation permitting a clear understanding of the issue and representing a means of searching and screening relevant Form FDA 483s for endotoxin-related issues.

2.2 Form FDA 483 Data Extraction and Categorisation

Form FDA 483s were acquired from 2011 up to and including 2021 by performing an SQL query for observation text terms 'endotoxin', 'contaminat' (this ensured terms contaminant, contaminate and contamination were included) and 'specification'. Data were downloaded into Microsoft® Excel. Each observation text was reviewed to check for relevancy. To assist with evaluation and trending of the cGMP violations, each Form FDA 483 was additionally categorised using the following terms:

2.2.1 Origin

Distinguishing between laboratory (including specification related), manufacturing and supplier sources of the cGMP violation.

2.2.2 Classification

Describing high-level root cause including controls (laboratory and manufacturing), adequacy of testing and test data, adequacy of investigations, manufacturing issues, sufficiency

of risk assessment, specifications, training of personnel and validations.

2.2.3 Product Type

Assigning a context to each record in terms of drug, device, test kit or active pharmaceutical ingredient related.

2.2.4 Test Sample

Associating each cGMP violation with a specific material including but not limited to water, raw material, finished drug product and manufacturing equipment.

2.2.5 Relevancy to Potential Endotoxin Quality Issues

Confirming the relevancy to endotoxin-related quality issues.

2.2.6 Potential to Release a Product That Impacts Patients

Evaluating each cGMP violation's potential to adversely affect patients.

2.3 FDA Drug and Device Recalls

The FDA publishes data for all drug and device recalls. The FDA's database for enforcement [16] reports all endotoxin-related drug and device recalls including all relevant information.

2.4 Drug and Device Recalls Data Extraction

The FDA enforcement database was accessed, and all recalls associated with endotoxins acquired from 2012 up to and including 2021 by performing an SQL query. The SQL query used the text term 'endotoxin' segmented into drug, device and biologics and data were downloaded into Microsoft® Excel. These data were additionally categorised by the reason for the recall including exceeding specification, failure of manufacturing controls, potential contamination from manufacturing and raw materials, and testing and failure to follow investigational requirements.

2.5 FAERS Database and Datasets

The FAERS database provided the AE data for this study. The informatic structure of the FAERS database is highly interactive, web based, permits querying of drug and medical device safety data, and complies to the international safety reporting guidance per the International Conference on Harmonization [29].

The FAERS includes AE report information separated into 24 data columns capturing details that include the suspect product (drug or device), the reason for product administration, associated reactions, event date, patient age and weight, and the country where the event occurred. The reactions column provides significant details concerning the patient symptoms and categorisation into clinical diagnoses permitting an assessment of any potential drug- and/or device-borne endotoxin issues.

2.6 FAERS Data Extraction

The FAERS database was accessed and AE data pertaining to fevers acquired from 2008 up to and including 2021 by performing an SQL query on all reports (serious reports and death). The SQL query used the text terms 'pyrexia', 'pyrexia infusion related', 'endotoxaemia', 'endotoxic shock', 'post procedural fever' and 'hyperpyrexia' within the 'reactions' data column to obtain the relevant AE data. Data were downloaded into Microsoft® Excel.

2.7 Statistical Analysis

Descriptive statistics in Microsoft Excel 2019 and pivot tables were used for the analysis and presentation of the data.

3 Results

3.1 Form FDA 483 Data

From 2011 to 2021, a total of 188 Form FDA 483 observations were generated from routine inspections of drug and device manufacturers associated with endotoxins (Table 1). Generally, most observations were associated with the laboratory (70%) followed by manufacturing (30%) and rarely associated with suppliers (< 1%). Singularly, in 2018, there was a 5- to 13-fold increase in endotoxin-related Form FDA 483s compared with other years inspectional observations. This abrupt increase in endotoxin-related observations, primarily attributed to laboratory non-compliances, was not indicative of a progressive industry-wide increase in patient safety risks.

Classification distribution (the category of origin which the inspectional observation falls into) year to year over 2011–2021 was generally consistent across the 14 different categories (Table 2). An exception occurred in 2019 where the total increase of Form FDA 483s was accompanied by increases in specific areas of classification. Those areas were investigations (inadequate or missing), laboratory testing Standard Operating Procedure (SOP) (inadequate for the sampling, storage and testing of samples), test data (missed testing or missing data), and inadequate or missing validations primarily for endotoxin testing (Table 2). Of the 188

Table 1 Endotoxin-related Form FDA 483s from October 2011 to October 2021 segmented by origin and compared to total numbers of Form FDA 483s and inspections

Year	Endotoxin-related 483s by origin				Total 483s issued[a]	Endotoxin-related 483s as a percentage of total 483s (%)	Total inspections (including food related)[b]	Endotoxin-related 483s as a percentage of all inspections (%)
	Laboratory	Manufacturing	Supplier	Total				
2011	5	4		9	2364	0.4	20,095	0.04
2012	7	5		12	2375	0.5	19,962	0.06
2013	10	3	1	14	2340	0.6	17,434	0.08
2014	1	6		7	2116	0.3	16,632	0.04
2015	3	3		6	2120	0.3	16,681	0.04
2016	6	5		11	2022	0.5	17,142	0.06
2017	7	3		10	2114	0.5	17,891	0.06
2018	4	3		7	2003	0.3	17,870	0.04
2019	66	12		78	1963	4.0	16,136	0.48
2020	16	2		18	908	2.0	7840	0.23
2021	6	10		16	534	3.0	6458	0.25
Total	131	56	1	188	20,859	0.9	174,141	0.11

FDA Food and Drug Administration

[a]https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations

[b]https://datadashboard.fda.gov/ora/cd/inspections.htm

Table 2 Endotoxin-related Form FDA 483s from October 2011 to October 2021 segmented by the classification the inspectional observation falls into

Classification	Year											Total
	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	
CAPA								1				1
Investigation	1	4		1	2	1	5	2	10	1	3	30
Laboratory controls	1					2			4			7
Laboratory testing SOP	1	2		1		1	2	3	15	7	2	34
Manufacturing controls			1	2		1	1		2	1		8
Manufacturing SOP											1	1
Risk analysis			1								1	2
Specifications									1			1
Data integrity			1						9	1		11
Test data		4	4		1	4	1	1	17	4	1	37
Data out of specification	3	1		1					3			8
Training									1			1
validation	2	2	7	2	3	2	1		16	5	7	47
Grand total	8	13	14	7	6	11	10	7	78	19	15	188

CAPA corrective and preventative action plan, *FDA* Food and Drug Administration, *SOP* standard operating procedure

Form FDA 483 observations, only one (0.5%) was due to inadequate specifications and eight (4.3%) were linked to product failing specifications.

Endotoxin-related Form FDA 483s segmented by classification of the inspectional observation demonstrated an overwhelming (56%) association with finished drug product testing (Table 3). From year-to-year 2011–21, the majority of Form FDA 483s were consistently associated with finished drug product testing and seldom with devices (Table 4). The notable increase in endotoxin-related inspectional observations peculiar to 2019 were predominantly linked to the testing of the finished drug product.

3.2 Drug and Device Recalls

The FDA enforcement data displayed in Table 5 clearly show that recalls associated with endotoxins are a negligible percentage of all recalls during 2012–2021. Of these

Table 3 Endotoxin-related Form FDA 483s segmented by the classification the inspectional observation falls into and the associated test samples

Classification	Test sample									
	API and raw materials	Container closure component	Process intermediates	Finished drug products	Devices	Manufacturing equipment	Laboratory (equipment, reagents)	Utilities	NA	Total
CAPA					1					1
Investigation	1		1	19	1	1	1	6		30
Laboratory controls				7						7
Laboratory testing SOP	1	1	2	22	1		2	4	1	34
Manufacturing controls	1	1	2	3					1	8
Manufacturing SOP		1								1
Risk analysis					1		1			2
Specifications				1						1
Data integrity				11						11
Test data	5	7		19	3	1	1	1		37
Data out of specification	1			7						8
Training				1						1
Validation	2	10	1	15	1	11	3	3	1	47
Grand total	11	20	6	105	8	13	8	14	3	188

CAPA corrective and preventative action plan, *API* active pharmaceutical ingredient, *FDA* Food and Drug Administration, *NA* not applicable, *SOP* standard operating procedure

Table 4 Endotoxin-related Form FDA 483s from October 2011 to October 2021 segmented by associated test sample

Test sample	Year											Grand total
	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	
API and raw material	2	1			1	2			2	2	1	11
Container, closure, component	1	3	4	1		1	1	1	4	2	2	20
Process intermediate				1			1		2	1	1	6
Finished drug product	4	5	6	2	2	5	6	4	56	12	3	105
Device			2	1	1		1	1	1		1	8
Manufacturing equipment		1	1	2	1				3		5	13
Laboratory (equipment, reagents)	1		1					1	3	1	1	8
Utilities		3			1	3	1		4	1	1	14
NA									3			3
Grand total	8	13	14	7	6	11	10	7	78	19	15	188

API active pharmaceutical ingredient, *FDA* Food and Drug Administration, *NA* not applicable

Table 5 Drug and device recalls 2012–2021

Product type	Recalls	Endotoxin-related recalls	Endotoxin-related recalls as % of total recalls
Biologics	10,785	2	0.019
Drugs	15,437	7	0.045
Devices	28,010	160	0.571
Total	54,232	169	0.312

recalls, devices account for 95% (160). The majority of recalls were performed because the marketed items were determined to be potentially contaminated during manufacturing (Table 6).

The number of endotoxin-related drug and device recalls per year were generally consistent over the 10-year period of 2012–21, averaging 10–20 each year (Fig. 1). In 2018, a total of 56 recalls were reported; 95% (53) were associated with devices and only two firms accounted for 88% (49) of these. This demonstrated a remarkably similar pattern to FDA Form 483s over the same duration; however, the non-compliance observations spiked in 2019 (Fig. 1).

3.3 FAERS Data

Adverse event data germane to fevers acquired from 2008 up to and including 2021 derived from the FAERS database are summarised in Table 7. Of 23,663,780 total AE, 326,921 (1.38%) could be attributed to adverse reactions that have been tagged with the term pyrexia in combination with many other reaction terms. The FAERS database contains > 1800 different combinations of reaction categories that include the term pyrexia and are indicative of pyrogenic responses linked to other causes of morbidity and not solely to drug- and medical device-borne bacterial endotoxins. Additional SQL queries of the FAERS database were performed to help address this and used the six text terms 'pyrexia', 'pyrexia infusion related', 'endotoxemia', 'endotoxic shock', 'post procedural fever' and 'hyperpyrexia' provided data, which are more representative of AEs associated with endotoxins. Although this refinement of SQL queries helps to achieve a dataset that more closely represents fever from drug- and device-borne endotoxin, it still includes reported fever attributable to the numerous other causes [22]. The totals for each AE therefore represent a worst-case tally; these data are reported in Table 7 and detailed below.

Table 6 Reasons for drug and device recalls 2012–2021

Reason for recall	Product type			
	Biologics	Drugs	Devices	Total
Exceeds specification	1	1	28	30
Failure of manufacturing controls		1	23	24
Failure to follow testing and investigation requirements		3	1	4
Failure to follow testing requirements			8	8
Potential contamination during manufacturing	1	2	91	94
Raw material contained high endotoxin			9	9
Total	2	7	160	169

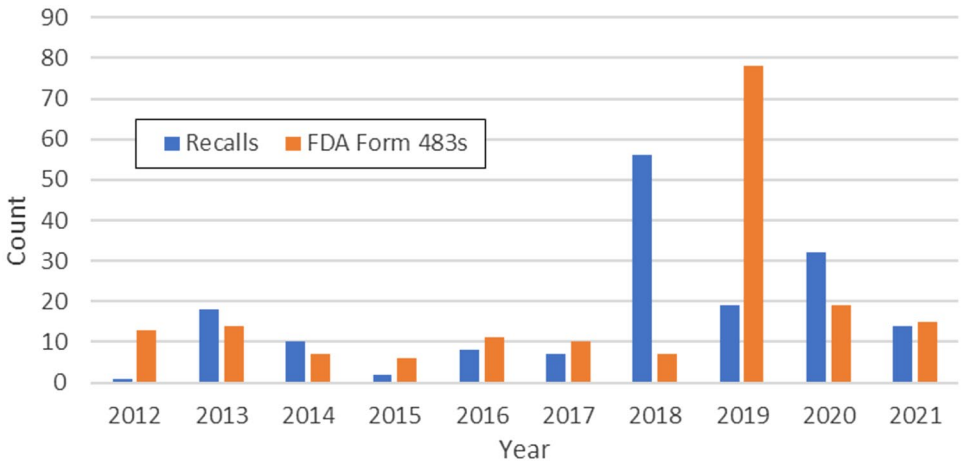

Fig. 1 Endotoxin-related drug (including biologics) and device recalls compared to Food and Drug Administration (FDA) Form 483s 2012–2021

Table 7 Analysis of the adverse events from the FDA Adverse Event Reporting System based upon search term from 2008 to December 2021

Search reaction term	Total reports	Serious reports	Death reports
All adverse event reaction terms	23,663,780	13,219,628	2,240,339
Pyrexia (in combination with other reaction terms)	326,921 [1.3815%]	266,122 [2.0131%]	6233 [0.2782%]
Pyrexia	15,824 [0.06687%]	9496 [0.07183%]	207 [0.00924%]
Pyrexia infusion related	30 [0.00013%]	18 [0.00014%]	0 [0%]
Endotoxemia	20 [0.00008%]	20 [0.00015%]	9 [0.00004%]
Endotoxic shock	96 [0.00040%]	95 [0.00072%]	48 [0.00214%]
Post-procedural fever	435 [0.00184%]	401 [0.00303%]	32 [0.00143%]
Hyperpyrexia	3123 [0.01320%]	3079 [0.02329%]	467 [0.02085%]

Values in square brackets are the number of events for each specific reaction term as a percentage of all reaction terms

3.3.1 Pyrexia

Pyrexia (otherwise known as fever) is an abnormal increase in body temperature. An adult's normal body temperature ranges from 97 °F (36.1 °C) to 99 °F (37.2 °C) and generally, onset of fever is regarded as ≥ 100 °F (38.3 °C) in adults. The total AEs reported solely as 'pyrexia' represented < 0.07% of all AEs. Review of these identified that at least 59% (9390) had sufficient information to categorically associate these cases of pyrexia with an illness or pre-existing condition. Therefore, the adjusted total of pyrexia reports of 6435 represents < 0.03% of all AEs.

3.3.2 Infusion-Related Pyrexia

Infusion-related pyrexia (distinct from transfusion pyrexia [30]) is a fever experienced by patients during the infusion of a therapy occurring on the first day of drug administration; appearing most frequently 10 minutes to 4 hours after the start of administration. There were 30 total cases reported as infusion-related pyrexia representing < 0.01% of the total AEs. Of these, 29 (97%) appear associated with an illness or pre-existing condition that could cause a febrile response.

3.3.3 Endotoxemia

Endotoxemia is clinically manifested as the presence of endotoxin within the blood and most usually associated with infection or pre-existing conditions. The occurrence of endotoxemia is extremely rare (0.00008%), although almost 50% of all reported cases resulted in mortality. From the FAERS data, eight of a total of 20 reported AE cases were associated with administration of the intravenous sedative propofolol, a drug that has been associated with fevers, chills and body aches but not necessarily associated with microbial contamination or endotoxins in the finished drug product [31].

3.3.4 Endotoxic Shock

Endotoxic shock is primarily associated with sepsis and septic shock induced by release of endotoxin into the bloodstream. The clinicopathology of endotoxic shock suggests that the FAERS data are not relevant to an assessment of

iatrogenic pyrexia caused by the administration of drugs and devices contaminated with endotoxin. Furthermore, the very rare percentage (0.00040%) of total AEs would suggest no association with drugs or devices.

3.3.5 Post-Procedural Fever

Post-procedural fever, also known as postoperative fever, is defined as a temperature higher than 38 °C (100.4 °F) on 2 consecutive postoperative days or higher than 39 °C (102.2 °F) on any postoperative day. Many parenterally administered drugs are known to cause fever in patients (see below); however, there are no reports to our knowledge linking this phenomenon with endotoxin levels associated with drugs or indwelling medical devices. The total cases of patient reactions reported as post-procedural fever represent <0.01% of total AEs.

3.3.6 Hyperpyrexia

Hyperpyrexia is the extreme elevation of the body temperature (>41.5 °C, >106.7 °F) and mostly associated with viral or bacterial infection. The severity of hyperpyrexia would argue that this phenomenon could not be solely induced by drugs or medical devices containing and contributing a high level of endotoxin. The total AEs reported solely as 'hyperpyrexia' represent <0.02% of all AEs.

4 Discussion

It is a reasonable assumption that any sign of significant inadequacies in the control, specifications and testing of drugs and devices for endotoxins would be reflected in Form FDA 483 observation data. Endotoxin-related cGMP non-compliances represent a very small percentage of all Form FDA 483 observations; furthermore, there are no apparent increasing trends in the quantity or specific types over the 11 years of analysis from 2011 to 2021. Non-compliance data and reports are suggestive that there is no patient safety risk associated with the establishment of drug and device endotoxin specifications per the compendial methodology. The noteworthy increase in endotoxin-related Form FDA 483 observations solely in 2019 is not easily explicable as no prior signal in cGMP non-compliances are evident. In recent years, the FDA has augmented its traditional inspectional processes with remote inspection practices. These conceivably might bias areas of focus; however, these practices were not embraced until after 2019. The increase in endotoxin-related device recalls in 2018 may have been the trigger for increased inspectional scrutiny in 2019, although inspectional observation data illustrate an emphasis on finished drugs and drug product testing rather than manufacturing controls. Significantly, the remarkable increase in Form FDA 483 observations in 2018, primarily associated with finished drugs is not accompanied by an increase in drug recalls in 2018 or beyond. Over the 10-year period of assessment (2012–2021), devices constitute 95% of all recalls with inadequate prevention of contamination or failed manufacturing controls accounting for these. All recalls data suggest no evidence of endotoxin-related issues with the finished drug product but rather device manufacturing firms recalling products in the absence of any cGMP inspectional observation trends. It might be argued that there appears some incongruity in the absence of FDA inspectional efforts (or at least Form FDA 483 observations data) focused on finished drug products, and the predominance of recalls associated with devices.

In terms of AEs, the phenomenon of fever can originate from a range of disparate physiological, metabolic and infectious sources. Although fever is regarded as a reliable hallmark of disease, it is no longer attributed to pathophysiological phenomena but is recognised as a generalised stress response [32]. Although the attribution of pyrexia solely and unequivocally to parenteral and medical devices contaminated with endotoxin is erroneous, any fevers due to drug- and device-related endotoxin is ensconced within pyrexia AE data. The complexity that fever is a general stress response may offer some explanation of the ambiguity to the exact cause of a reported fever. Infusion-related pyrexia is only one of many infusion-related reactions, which may be experienced during infusion of a drug [33]. Monoclonal antibodies are commonly associated with infusion-related reactions; however, if infusion-related reactions are encountered, they are very rarely fever alone, but rather one of a constellation of simultaneous reactions [33]. This likely provides a means of clinical distinction between infusion-related pyrexia due to a patient's reaction to the therapeutic molecule and pyrexia induced by the presence of endotoxins; only a single infusion-related pyrogenic AE appears iatrogenic. Although propofolol is a drug that has been associated with fevers, chills and body aches, these appear associated with inadequate and lax aseptic handling of opened drug containers [34]. The propofolol example serves to illustrate a very important point in that drug-related endotoxins are more likely due to inadequate controls in handling parenteral drugs in the clinic or at the bedside. Post-procedural fever is widely acknowledged as associated with pulmonary conditions, infections (e.g. urinary tract, surgical-site infections), deep-vein thrombosis, withdrawal from drugs, endocrine causes or drugs [35]. Again, the FAERS data are not indicative of drug- or device-associated pyrexia.

Pyrexia of unknown origin (PUO) is not a reaction category in the FAERS database, the phenomenon could be captured within several of the reaction categories and therefore deserves due consideration. The phenomenon

of PUO dates back to 1961; it was described as a persistent fever above 100 °F (38.3 °C) that evades diagnosis for at least 3 weeks, including 1 week of investigation in hospital [36]. The causes of PUO can be considered in four categories: infective, inflammatory, neoplastic and miscellaneous. The relative prominence of each category has changed over time, with an increasing proportion of patients who remain undiagnosed, which may be up to 51% of cases [37]. Infectious causes account for 17–35% of cases, inflammatory causes 24–36%, neoplastic causes 10–20% and miscellaneous causes 3–15% [38].

Fernandez and Beeching [39] have categorised the non-infectious sources of PUO and includes in this group a miscellaneous origin that includes 'drug fever'. These authors state that drug fever is an under-recognised cause of PUO, particularly in the elderly. Drug fever can occur at any time after starting a therapy (including several months later), but usually begins 7–10 days after starting a medication [40]. Drug-associated fever can be diagnosed by discontinuing the therapy; if fever persists for more than 96 hours after its discontinuation, then the suspected drug is unlikely to be the cause [41]. Many classes of medications can cause fever through different mechanisms including antibiotics, anticholinergics, non-steroidal anti-inflammatory drugs, allopurinol, anticonvulsants, anti-hypertensives, anti-arrhythmic agents and antidepressants. Remarkably, many authors [42, 43] do not identify the contamination of therapies or associated medical devices with endotoxin as candidates for PUO. Furthermore, the onset timing of pyrexia would not be consistent with the introduction of endotoxins from medications or indwelling devices. Based upon these data, PUO are most likely not due to the cumulative contribution of endotoxin from simultaneously administered drug products and devices, nor inappropriate endotoxin specifications. Yatabe et al. [44] commented on the drug fever case study associated with the intravenous sedative propofol arguing "*Propofol-induced drug fever must be considered in cases of fever of unknown origin when patients receive propofol and appear inappropriately well for the degree of fever that they have*". The same reasoning might be applied for any medication or medical device. Applying Yatabe et al.'s reasoning that pyrexia with limited or no other adverse manifestations is attributable to 'drug fever' supports this evaluation of AEs solely based upon pyrexia.

5 Strengths and Limitations

Although data reported through accessible Form FDA 483 observations documents a formal non-compliance as interpreted by the FDA, these reports fail to identify all potential endotoxin-related issues. This is somewhat due to the variability of interpretation and the FDA inspectional practices.

Even though reasonably comprehensive, the FAERS suffers limitations that include (but are not limited to) the absence of data verification, incomplete data, duplicated information and limitations on establishing causality. Although it is incumbent upon healthcare providers to report AEs, it has been estimated that up to 90% in clinical practice are unreported [45]. The FAERS data do not permit the unequivocal categorisation of fever-related AEs solely to drug- and device-borne endotoxin. The data do however include drug- or device-related endotoxin fevers and therefore the data represent a worst case set of information.

6 Conclusions

Evaluation of the contention that finished drug product- and device-borne endotoxin (and concomitantly the compendial method of establishing endotoxin specification limits) represents a tangible patient safety risk demands the assessment of data from multiple and disparate sources. Here, the triumvirate analysis of industry's compliance to associated regulations (derived from FDA inspectional data), the extent of product recalls associated with endotoxins coupled with AE data represented such an assessment. Based on the available data, and notwithstanding the stated limitations, there appears few data substantiating wide pyrogenic responses from drug- and device-borne endotoxins post hoc to their administration.

In 2000, a report estimated that 16 billion injections were administered per annum in developing countries [46]. It would not be unrealistic to estimate the administration of 1 billion parenteral drugs administered in the USA over 14 years. As a worst case, assuming that all reported pyrogenic AEs (15,824) were due to drug- and device-borne endotoxin, this would equate to an AE rate of 70 in every million parenteral administrations. This would be regarded as very rare.

The provision of safe parenteral drugs and devices is fundamentally reliant upon cGMP controls and tests founded upon sound scientific principles. Deviation from this in the application of controls and tests that are in good faith aimed at further reducing patient safety risk yet are arbitrary in nature removes the further principled continuity of improvement. Considering the data herein, there appears no basis to any industry-wide patient safety risk from drug- or device-borne endotoxins, means of establishing specification or compendial test methodology. This would seem to corroborate the work of Pearson [47] who

demonstrated through numerous studies that there exists at least an eight-fold safety margin within the compendial methods of specification setting and testing. Nevertheless, opportunities do exist for principle-based improvements such as the use of a statistical basis of body weights in establishing endotoxin specifications, a contemporary review of newer innovative medical devices and a focused effort on endotoxin control during parenteral manufacture.

Declarations

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Conflicts of interest/competing interests The author declares no conflicts of interest that are directly relevant to the content of this study. Edward C. Tidswell is a member of the USP, General Chapters-Microbiology Expert Committee.

Ethics approval Ethics approval was not needed for this study.

Consent to participate No patient approval or consent was needed for this study.

Consent for publication No patient approval or consent was needed for this study.

Availability of data and material Datasets concerning drug and device recalls and AEs in this article are publicly available and can be obtained through the following sources: FDA Enforcement Reports (drug and device recalls): https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/enforcement-reports; FAERS: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard. Datasets concerning Form FDA 483 observations (cGMP non-compliance observations) for this article are not publicly available because they are part of a fee-paying services provided by Redica Systems and are available from the corresponding author on reasonable request.

Code availability Not applicable.

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