American Pharmaceutical
Review
The Review of American Pharmaceutical Business & Technology

Volume 22 Issue 6 | September/October 2019

SHOW ISSUE:

PDA's 14th Annual Global Conference on Pharmaceutical Microbiology

AAPS PharmSci360

Eastern Analytical Symposium & Exposition

Analysis of FDA Enforcement Reports (2012-2019) to Determine the Microbial Diversity in Contaminated Non-Sterile and Sterile Drugs

Progress in the Development of Aqueous Two-Phase Systems Comprising Ionic Liquids for the Downstream Processing of Protein-Based Biopharmaceuticals

A Roadmap for Implementing QRM Principles in Drug Substance Manufacturing

www.americanpharmaceuticalreview.com

Analysis of FDA Enforcement Reports (2012-2019) to Determine the Microbial Diversity in Contaminated Non-Sterile and Sterile Drugs

Luis Jimenez

Biology and Horticulture Department
Bergen Community College, Paramus, NJ

Abstract

An analysis of FDA enforcement reports from 2012 to 2019 showed that Gram-negative bacteria were the most common microbial contaminants of non-sterile drugs in the United States. *Burkholderia cepacia* was the number one reason for non-sterile drug recalls with 102 citations followed by *Ralstonia pickettii* (45 recalls) and the USP indicator, *Salmonella* spp. (28 recalls). Unidentified microbial contamination accounted for 77% of non-sterile and 87% of sterile drug recalls indicating extremely poor microbiology practices. The presence of yeast and mold was the reason for 52 recalls of sterile and non-sterile drugs with only 12% providing any information at the genus or species level. Gram-negative bacteria were the most common cause of microbial contamination for sterility failures with no species showing a predominant presence. However, out of specification results (34 recalls) were the most cited violation for non-sterility recalls. Most sterile drugs (1056) were recalled by the lack of sterility assurance. Undetermined cGMP issues (184 recalls) was the number one reason for lack of sterility assurance followed by compounded drugs with deficient cGMP procedures (121 recalls).

Introduction

The Food and Drug Administration (FDA) is the federal agency responsible for the regulation of pharmaceutical products in the United States of America (USA). The FDA oversees the development, manufacturing, and use of drugs by developing guidelines and regulations to guarantee safety, stability, and efficacy. Enforcement activities by the FDA range from warning letters and notice of violation letters to pharmaceutical companies. When drugs are recalled because stability, safety, or efficacy are compromised, the agency issues an enforcement report. Microbial contamination is one of the major reasons for recalls in the USA.

Microbial contamination control is a fundamental requirement for sterile and non-sterile manufacturing of pharmaceutical drugs. Non-sterile pharmaceuticals are manufactured under conditions to

minimize microbial contamination but the processes used during production are not monitored on a regular basis.[1,2] Furthermore, the criteria for manufacturing non-sterile pharmaceuticals are completely different when compared to sterile products because of the lack of regulatory or compendial guidelines. However, according to the Code of Federal Regulations (CFR) part 211.113, companies must have appropriate written procedures, designed to prevent the presence of objectionable organisms from drug products not required to be sterile.[3] This includes standard operating procedures (SOP's) for manufacturing and quality control analysis for each non-sterile product. Written procedures for manufacturing, packaging, and quality control analysis allow reproducibility, continuity, accuracy, and process control. For instance, in sterile manufacturing, water, air, analysis, and environmental monitoring are performed on a routine basis preventing sterility failures and system breakdown. However, non-sterile manufacturing does not monitor these areas, if they monitor them at all, as frequently as sterile processes.[2] Some companies performed environmental monitoring of production facilities and equipment sporadically while others did not do it on a regular basis or none at all.[2] Current good manufacturing practices (cGMP) control the presence, viability, and proliferation of microorganisms. However, pharmaceutical companies follow different strategies during the manufacturing of non-sterile products. Furthermore, microbial identification of environmental isolates from non-sterile manufacturing environments varies from company to company. Some companies had a vigorous microbial identification program but others relied on simple identification schemes.[2,4] Because of the infrequent and inconsistent monitoring of equipment, personnel, and environment, microbial identification from raw materials and finished products is a critical step for the quality control analysis of non-sterile pharmaceuticals. Major deviations from cGMP have been currently observed in several locations responsible for the manufacturing of non-sterile pharmaceutical products.[5-7] Those deviations have not only led to major product recalls but also serious incidents of morbidity and mortality.[5,6,8]

Underwood[9] clearly stated, "The microbiological quality of pharmaceutical products is influenced by the environment in which they are manufactured and by the materials used in their formulation". If the product is not terminally sterilized, the finished product bioburden will include microbial flora from raw materials, equipment, air, personnel, and containers. Optimization of microbial contamination control requires the development and implementation of adequate systems controlling environmental conditions where product manufacturing will take place. When these systems are absent, failed, or are not validated, the manufacturer suffers by the positive evidence of objectionable microorganisms or high microbial counts in the finished product.

Jimenez[10] reported the first comprehensive analysis to determine the microbial diversity in contaminated medical devices, non-sterile, and sterile drugs.[10] Data collection and analysis were time consuming, repetitive, and slow. Furthermore, the information was disseminated through FDA enforcement reports, published scientific studies, and industry newsletters. Recall data showed that *Burkholderia cepacia* contaminated more sterile and non-sterile drugs than any other microbial species while yeast and mold contamination was found to be a major problem during manufacturing. Contamination by Gram-negative bacteria appeared to be more prevalent than with Gram-positive bacteria. Large numbers of drug and medical device recalls did not provide any microbial identification at the genus or species level.[10] Most medical devices and sterile drugs were recalled due to the lack of sterility assurance (LSA). Sutton and Jimenez[11] provided a later update looking only at enforcement reports listed on the FDA website for the years 2004-2011 and reported similar findings regarding microbial identification, LSA, *B. cepacia* and mold contamination. Ever since then, the website has been significantly improved with new analytical tools to improve data mining and transparency of the different enforcement reports.

The major objective of this article is to analyze FDA enforcement reports by determining the sources of microbial contamination in non-sterile and sterile drugs from the years 2012 to 2019 and to determine if there are any changes compared to previous years. The information used for this article is listed on the FDA website regarding enforcement reports and was collected using the advance search engine:

(https://www.accessdata.fda.gov/scripts/ires/index.cfm#tabNav_advancedSearch). The recall information was restricted to enforcement reports issued from June 8, 2012 to June 21, 2019. The databases analyzed were limited to non-sterile and sterile drugs. Excel spreadsheets were used for data mining and analysis.

Table 1. Microbial identification in recalls of raw materials, non-sterile (NS) and sterile (S) drugs (1995-2019).

Microorganism	2012-2019	2004-2011[11]	1995-2006[10]
Achromobacter xylosoxidans	1 S	1 NS	0
Aspergillus spp.	4 S	1 NS	0
Aspergillus fumigatus	1 NS	0	0
Bacillus circulans	1 S	0	0
Bacillus thuringiensis	1 S	0	0
Burkholderia cepacia.	102 NS	35 NS	35 (30 NS, 5 S)
Burkholderia contaminans	1 NS	0	0
Burkholderia gladioli	1 NS	0	0
Burkholderia multivorans	1 NS	0	0
Clostridium difficile	13 NS	0	0
Escherichia coli	2 NS	1 NS	0
Herbaspirillum huttiense	1 S	0	0
Klebsiella pneumoniae	1 S	0	0
Paecilomyces saturatus	1 NS	0	0
Pseudomonas spp.	1 NS	2 NS	0
Pseudomonas aeruginosa	2 NS	7 NS	20 (19 NS, 1 S)
Ralstonia pickettii	45 NS	0	3 (2 NS, 1 S)
Rhinocladiella similis	1 NS	0	0
Salmonella	28 NS	2 NS	6 NS
Sarcina lutea	1 NS	0	0
Serratia liquefaciens.	6 NS	0	0
Staphylococcus aureus	2 NS	1	0
Staphylococcus saprophyticus	4 NS	0	0
Staphylococcus warneri	1 S	1 NS	0
Sphingomonas paucimobilis	2 (1 NS, 1S)	0	0
Variovorax paradoxus	1 S	0	0

Bacterial Contamination of Non-Sterile Pharmaceutical Samples

An analysis of non-sterile pharmaceutical products recalled by the FDA from the years 2012-2019 demonstrated that, of the United States Pharmacopeia (USP) microbial indicators, 28 recalls were due to the presence of *Salmonella* spp. (Table 1). Table 1 shows data comparison with previous studies published in 2007 and 2012.[10,11] Compared to what was reported for the years 2004-2011, the number of recalls by *Salmonella* spp. increased from two to 28.[11] The numbers for 1995-2006 were also lower with only six recalls issued due to the presence of Salmonella (Table 1).[10]

Salmonella spp. contaminated raw materials and products such as pain relievers (Table 2). Bacterial identification was limited to the genus level with no species reported. Contamination was probably caused from raw materials that were not properly qualified with a validated microbial method to determine the microbial load or a manufacturing process that was not optimized to eliminate pathogenic microorganisms.[1] *Mitragyna speciosa* is a tropical evergreen tree commonly known as Kratom. All contaminated samples were either Kratom raw material or formulations based upon the ingredient. Kratom is a natural product and as such, it may contain a high microbial load. The production processes for this raw material do not eliminate all microorganisms. However, an optimized manufacturing process can be designed to eliminate Salmonella from products and raw materials.[1,9-11]

Why was *Salmonella* spp. a reason to recall products and raw materials? The three major pharmacopoeias, USP, European (EP), and Japanese (JP) have divided non-sterile pharmaceuticals testing into two different tests: The quantitative test and qualitative test.[1] The quantitative test ascertains the numbers of microorganisms, e.g., bacteria, yeast, and mold, present in a given pharmaceutical sample. The qualitative test determines the presence of specific pathogen indicators, e.g., *Salmonella* spp., *Escherichia coli*, *Candida albicans*, *Clostridium* spp., *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and the Enterobacteriaceae family, which might cause disease to consumers or indicate the presence of other pathogenic bacteria. These indicators are representative microbial species of different types of bacterial populations. For instance, *E. coli* is a Gram-negative rod, capable of lactose fermentation, commonly found in fecal sources. *Salmonella* spp. are virulent Gram-negative rods associated to intestinal disorders

Table 2. Drug recalls for non-sterile products and raw materials based upon FDA enforcement reports (June 2012-2019) (n=163). Cont'd

Number	Product	Reason for Recall
1	Zicam Extreme Congestion Relief (oxymetazoline HCl) Nasal Gel	Microbial Contamination of Non-Sterile Products: Product may be contaminated with *Burkholderia cepacia*.
2	Diocto Liquid (docusate sodium) Stool Softener Laxative	Microbial contamination of Non-Sterile Products; positive findings of *Burkholderia cepacia*.
3	Docusate Oral Oral Syringe	Microbial Contamination of Non-Sterile Products; microbial contamination with *B. cepacia*.
4	Dimethicone Barrier Cream Cloths	Microbial Contamination of Non-Sterile Products: contamination with the bacteria, *Burkholderia cepacia*.
5	Compulsin, Homeopathic (OTC Medicine)	Microbial Contamination of Non-Sterile Products; Products contaminated with microoganisms, including but not limited to *Staphylococcus saprophyticus* and *Burkholderia cepacia*
6	Neuroveen, Homeopathic (OTC Medicine)	Microbial Contamination of Non-Sterile Products; Products contaminated with microoganisms, including but not limited to *Staphylococcus saprophyticus* and *Burkholderia cepacia*
7	Thyroveev, Homeopathic (OTC Medicine)	Microbial Contamination of Non-Sterile Products; Products contaminated with microoganisms, including but not limited to *Staphylococcus saprophyticus* and *Burkholderia cepacia*
8	Respitrol, Homeopathic (OTC Medicine)	Microbial Contamination of Non-Sterile Products; Products contaminated with microoganisms, including but not limited to *Staphylococcus saprophyticus* and *Burkholderia cepacia*
9	Antiseptic Wipes, First Aid Antiseptic, Benzalkonium Chloride	Microbial contamination of Non-Sterile Product; contamination with *Burkholderia cepacia* (manufacturer)
10	Swab, First Aid Antiseptic, (Benzalkonium Chloride)	Microbial contamination of Non-Sterile Product; contamination with *Burkholderia cepacia* (manufacturer)
11	Luxury Foam Hand Sanitizer, (Benzalkonium Chloride)	Microbial Contamination of Non-Sterile Products; The affected lots were found to be contaminated with bacterium, *Burkholderia cepacia* complex.
12	Foam Hand Sanitizer, Alcohol Free	Microbial Contamination of Non-Sterile Products; The affected lots were found to be contaminated with bacterium, *Burkholderia cepacia* complex.
13	Sennazon (sennosides) Syrup	cGMP Deviations: Recall initiated as a precautionary measure due to a potential risk of product contamination with the bacteria *B. cepacia*.
14	Ninjacof (Chlophedianol HCl and Pyrilamine Maleate) Liquid	cGMP Deviations: Recall initiated as a precautionary measure due to a potential risk of product contamination with the bacteria *B. cepacia*.
15	Ninjacof-A (Acetaminophen, Chlophedianol HCl, Pyrilamine Maleate) Liquid	cGMP Deviations: Recall initiated as a precautionary measure due to a potential risk of product contamination with the bacteria *B. cepacia*.
16	Chlorpheniramine Maleate Syrup	cGMP Deviations: Recall initiated as a precautionary measure due to a potential risk of product contamination with the bacteria *B. cepacia*.
17	Diocto Syrup (Docusate Sodium)	cGMP Deviations: Recall initiated as a precautionary measure due to a potential risk of product contamination with the bacteria *B. cepacia*.
18	Senexon Liquid (Sennosides)	cGMP Deviations: Recall initiated as a precautionary measure due to a potential risk of product contamination with the bacteria *B. cepacia*.
19	Senna Syrup (Sennosides)	cGMP Deviations: Recall initiated as a precautionary measure due to a potential risk of product contamination with the bacteria *B. cepacia*.
20	Nystatin Oral Suspension	cGMP Deviations: Purified water used to manufacture the drug products may have been contaminated with *Burkholderia cepacia*.
21	Hydrocodone Bitartrate and Acetaminophen Oral Solution	cGMP Deviations: Purified water used to manufacture the drug products may have been contaminated with *Burkholderia cepacia*.
22	Metoclopramide Oral Solution	cGMP Deviations: Purified water used to manufacture the drug products may have been contaminated with *Burkholderia cepacia*.
23	Phenytoin Oral Suspension	cGMP Deviations: Purified water used to manufacture the drug products may have been contaminated with *Burkholderia cepacia*.
24	Nystatin Oral Suspension	cGMP Deviations: Purified water used to manufacture the drug products may have been contaminated with *Burkholderia cepacia*.
25	Lactulose Solution	cGMP Deviations: Purified water used to manufacture the drug products may have been contaminated with *Burkholderia cepacia*.
26	Lactulose Solution	cGMP Deviations: Purified water used to manufacture the drug products may have been contaminated with *Burkholderia cepacia*.
27	Oxycodone Hydrochloride Oral Solution	cGMP Deviations: Purified water used to manufacture the drug products may have been contaminated with *Burkholderia cepacia*.
28	Methadone Hydrochloride Oral Concentrate	cGMP Deviations: Purified water used to manufacture the drug products may have been contaminated with *Burkholderia cepacia*.
29	Methadone Hydrochloride Oral Concentrate	cGMP Deviations: Purified water used to manufacture the drug products may have been contaminated with *Burkholderia cepacia*.
30	Methadone Hydrochloride Oral Concentrate	cGMP Deviations: Purified water used to manufacture the drug products may have been contaminated with *Burkholderia cepacia*.
31	Lactulose Solution	Microbial Contamination of Non-Sterile Products: bulk solution tested positive for the presence of the bacteria, *Burkholderia cepacia*.
32	Liquid, Docusate Sodium Stool Softener Laxative	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination
33	Syrup, Docusate Sodium, Stool Softener Laxative	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination

Table 2. Drug recalls for non-sterile products and raw materials based upon FDA enforcement reports (June 2012-2019) (n=163). Cont'd

Number	Product	Reason for Recall
34	Syrup Natural Vegetable Laxative, Sennoside	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination
35	Chlorpheniramine Maleate Syrup	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination
36	Liquid Natural Vegetable Stimulant	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination
37	Liquid, Docusate Sodium, Stool Softener Laxative	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination
38	Syrup, Docusate Sodium, Stool Softener Laxative	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination
39	Liquid Natural Vegetable Stimulant	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination
40	Chlorpheniramine Maleate Syrup	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination
41	Chlophedianol HCL and Pyrilamine Maleate Oral Solution	Microbial contamination of Non-Sterile Products; potential *B. cepacia* contamination
42	Acetaminophen, Chlophedianol HCL, Pyrilamine Maleate Oral Solution, Cotton Candy Flavor,	Microbial contamination of Non-Sterile Products; potential *B. cepacia* contamination
43	Allergy & Decongestant Relief (Diphenhydramine Hydrochloride and Phenylephrine Hydrochloride) Syrup	cGMP Deviations: Recall initiated as a precautionary measure due to a potential risk of product contamination with the bacteria *B. cepacia*.
44	Cough & Cold (Diphenhydramine Hydrochloride and Phenylephrine Hydrochloride) Syrup	cGMP Deviations: Recall initiated as a precautionary measure due to a potential risk of product contamination with the bacteria *B. cepacia*.
45	Codeine-Guaifenesin Oral Solution, Antitussive Expectorant	Microbial Contamination of Non-Sterile Products: potentially contamination with the bacteria *Burkholderia cepacia*
46	Children's Pain & Fever Acetaminophen, Pain Reliever/Fever Reducer, Single-Use Vials Cherry Flavor	cGMP Deviations: Recall as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*.
47	Children's Mucus Relief Chest Congestion Plus Cough Dextromethorphan HBr Cough Suppressant Guaifenesin Expectorant Mixed Berry Flavor 20 Singe-Use	cGMP Deviations: Recall as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*.
48	Diphenhydramine HCl Antihistamine, Pre-Measured Single-Use Vials, Mixed Berry	cGMP Deviations: Recall as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*.
49	Children's Pain & Fever Oral Solution Acetaminophen, Pre-Measured Single-Use Cherry Flavor	cGMP Deviations: Recall as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*.
50	Children's Allergy Relief Liquid Medication Diphenhydramine HCl Oral Solution Antihistamine Mixed Berry Flavor	cGMP Deviations: Recall as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*.
51	Children's Cough & Chest Congestion DM, Dextromethorphan HBr Guaifenesin Mixed Berry Flavor	cGMP Deviations: Recall as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*.
52	Children's Cough Syrup English Ivy Leaf Daytime Relief Natural Pineapple Flavor	cGMP Deviations: Recall as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*.
53	Children's Natural Cough Syrup English Ivy Leaf Organic Agave Nectar	cGMP Deviations: Recall as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*.
54	Children's Nasal Saline Drops with Himalayan Salt Saline Nasal Moisturizer	cGMP Deviations: Recall as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*.
55	Himasal Natural Nasal Saline Solution with Himalayan Salt	cGMP Deviations: Recall as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*.
56	Children's Cough & Chest Congestion DM Dextromethorphan HBr, Cough Suppressant Guaifenesin, Expectorant Mixed Berry Flavor	cGMP Deviations: Recall as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*.
57	RisperiDONE Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
58	Acetaminophen Liquid, Fever and Pain, Alcohol Free, Aspirin Free, Ibuprofen Free, Cherry Flavor	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
59	Allergy Liquid Antihistamine, Diphenhydramine HCl, Alcohol Free	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
60	Acetaminophen Liquid, Fever Reducer, Pain Reliever, Alcohol Free, Aspirin Free, Cherry Flavored, Acetaminophen	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
61	Cough Formula Expectorant Guaifenesin	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
62	Guaifenesin and Codeine Phosphate Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
63	Syrup, Dextromethorphan HBr, and Guaifenesin,	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
64	Oral Solution, Sugar Free, Alcohol Free, Cherry Flavor, (Diphenhydramine HCl, USP)	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
65	Pseudoephedrine Oral Solution, Nasal Decongestant	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
66	Nasal Decongestant Spray Regular, Oxymetazoline HCl 0.05%	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
67	Cough Sugar-Free Clear Cough Expectorant (Dextromethorphan HBr), Expectorant (Guaifenesin)	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
68	Cough-Cold Oral Solution, Alcohol Free, Antihistamine, Cough Suppressant, Nasal Decongestant, Chlorpheniramine Maleate; Dextromethorphan HBr; Pseudoephedrine HCl	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.

Table 2. Drug recalls for non-sterile products and raw materials based upon FDA enforcement reports (June 2012-2019) (n=163). Cont'd

Number	Product	Reason for Recall
69	Biscolax Laxative (Bisacodyl)	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*. *Burkholderia cepacia*
70	Cyproheptadine Hydrochloride Syrup Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
71	Hyoscyamine Oral Drops	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
72	Hyoscyamine Sulfate Elixir	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
73	Cetirizine HCL Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
74	Acetic Acid Otic Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
75	Guaifenesin AC Cough Syrup (Guaifenesin and Codeine Phosphate Oral Solution)	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
76	Guaifenesin DAC Oral Solution, Sugar Free, (Guaifenesin, Pseudoephedrine HCl and Codeine Phosphate Oral Solution), Expectorant, Nasal Decongestant, Cough Suppressant	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
77	Phenobarbital Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
78	Pain & Fever Oral Solution (Acetaminophen 160 mg/5 mL), Sugar Free, Aspirin & Alcohol Free, Cherry Flavored	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
79	Childrens Cough/Cold Liquid, Antihistamine, Cough Suppressant, Nasal Decongestant, Cherry Flavored, Alcohol Free, (Chlorpheniramine Maleate, Dextromethorphan HBr, Pseudoephedrine HCl),	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
80	Cough Syrup (Guaifenesin Syrup), Alcohol Free Non-Narcotic Expectorant	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
81	Extra Action Cough Syrup (Guaifenesin and Dextromethorphan HBr Syrup)	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
82	Diphenhist Oral Solution (Diphenhydramine HCl)	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
83	Nasal Decongestant Liquid, Pseudoephedrine HCl	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
84	Lactulose Solution, For Oral Administration	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
85	Lactulose Solution, For Oral or Rectal Administration	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
86	Memantine Hydrochloride Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
87	Memantine Hydrochloride Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
88	Hydrocortisone Acetate Suppositories	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
89	Laxative Suppositories (Bisacodyl)	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
90	Hemorrhoidal Suppositories (Phenylephrine HCl; Hard Fat)	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
91	Hemorrhoidal Suppositories (Phenylephrine HCl; Hard Fat)	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
92	Cetirizine Hydrochloride Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
93	Cetirizine Hydrochloride Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
94	RisperiDONE Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
95	Hydrocodone Bitartrate and Homatropine Methylbromide Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
96	Hydrocodone Bitartrate and Homatropine Methylbromide Oral Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
97	Bisacodyl Suppositories	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
98	Dextromethorphan HBr, Guaifenesin, Solution	cGMP Deviations: Potential product contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
99	Cetirizine HCL Oral Solution, Children's Allergy, Antihistamine, Dye Free, Gluten Free, Grape Flavor	cGMP Deviations: Potential contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
100	Cetirizine Oral Solution, Children's Allergy, Antihistamine, Dye Free, Grape Flavor	cGMP Deviations: Potential contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
101	Cetirizine Oral Solution, Children's allergy relief, Antihistamine, Dye Free, Grape Flavor	cGMP Deviations: Potential contamination with *Burkholderia cepacia* and *Ralstonia pickettii*.
102	Cetylpyridinium Chloride Mouthwash	Microbial Contamination of a Non-Sterile Products: Three product lots are contaminated with *Burkholderia cepacia*.
103	Diphenhydramine Hydrochloride Oral Suspension	Microbial Contamination of Non-Sterile Product(s): The product has the potential to be contaminated with *Burkholderia multivorans*.
104	Alcohol Free (Cetyl Pyridinium Chloride) Antiseptic Mouth Rinse	Microbial Contamination of Non-Sterile Product(s): The product has the potential to be contaminated with *Burkholderia contaminans*.
105	Antiseptic Anesthetic, Benzalkonium Chloride, Lidocaine Hydrochloride	Microbial Contamination of Non-Sterile Product(s): The product has the potential to be contaminated with *Bulkholderia gladioli*.

while *E. coli* in general is not a virulent pathogen. However, some strains of *E. coli* are producers of toxins associated to gastrointestinal diseases. *C. albicans* is the most prevalent cause of fungal infections in people. *Clostridium* is a genus of Gram-positive anaerobic bacteria, which includes several significant human pathogens such as *C. botulinum*, *C. difficile*, *C. perfringens*, and *C. tetani*.

Pseudomonas aeruginosa is a Gram-negative non-fermentative rod, which is typically associated to opportunistic infections. *S. aureus*, a Gram-positive coccus, is commonly associated to skin, pneumonia, gastrointestinal, and toxic shock syndrome conditions. Some strains of *S. aureus* known as Methicillin-Resistant *Staphylococcus aureus* (MRSA) are nosocomial pathogens.

The Enterobacteriacae family, also known as bile-tolerant bacteria, comprises Gram-negative genera such as *Escherichia, Salmonella, Shigella, Citrobacter, Enterobacter, Klebsiella, Proteus*, etc. Most of the members of this family, other than *Salmonella* spp. and *Shigella* spp., are opportunistic pathogens widely distributed in the environment. The use of pathogen indicators does not mean that the presence of other objectionable bacteria might not be a problem during quality evaluations. However, route of application and intended use of a given product will determine if there is a risk involved when other microorganisms are present.[10,11]

Other USP microbial indicators were cited in non-sterile recalls. *C. difficile* contaminated thirteen different samples (Table 1). The samples were laxative formulations and raw materials (Table 2). Contamination in raw materials such as Psyllium and lime bone gelatin promoted microbial growth in the formulations. Psyllium is a form of fiber made from the husks of the *Plantago ovata* plant's seeds. The gelatin is a varied ingredient with many applications in dietary supplements and pharmaceuticals. There was no recall of non-sterile drugs by *C. difficile* or any other *Clostridium* species before 2011 (Table 1).

E. coli contaminated two samples, e.g., antacids and throat relief formulations (Table 2). *E. coli* contaminated one sample back in 2004-2011.[11] *Pseudomonas aeruginosa* contaminated two samples of nasal decongestant liquids and hand sanitizer foams. *Pseudomonas* spp. contaminated one sample of heartburn relief medications. *P. aeruginosa* numbers were higher for the years 2004-2011. Nine recalls were issued due to contamination with *P. aeruginosa* and other *Pseudomonas* species (Table 1). However, in 1995-2006 enforcement reports cited *P. aeruginosa* nineteen times and other *Pseudomonas* species thirteen times (Table 1).[10] One recent recall cited the presence of the Gram-negative species, *Sphingomonas paucimobilis* (Table 2).

Other members of the Enterobacteriacae family detected were *Serratia liquefaciens* with six recalls of hand sanitizer sprays without alcohol as the only products affected (Tables 1 and 2). Different species of *Serratia* were found in previous studies with lower recall numbers by *S. fonticola* and *S. marcescens*.[11] Compared to what was reported by Jimenez[10] and Sutton and Jimenez,[11] *Enterobacter* species such as *E. gergoviae* and *E. cloacae* did not contaminate any drugs.

Staphylococcus species contaminated six samples of products and raw materials with two samples showing *S. aureus*, a USP indicator, and four samples with *S. saprophyticus*. *S. saprophyticus* was always isolated with *B. cepacia* (Table 2). Only one recall was issue in 2004-2011 due to *S. aureus* contamination. A recent recall cited the presence of the Gram-positive species, *Sarcina lutea* (Tables 1 and 2).

B. cepacia is Still the One!

B. cepacia was again the number one microbial species contaminating non-sterile drugs. Enforcement data cited *B. cepacia* in 102 recalls (Table 1). *B. cepacia* was previously reported to be the main reason for product recalls in 1995-2006 and 2004-2011.[10,11] Enforcement reports showed 30 and 35 recalls, respectively (Table 1). An average of thirteen recalls per year in 2012-2019 were calculated with more than 50% issued in the first half of 2019 (Table 3). That can be because of an increase in enforcement activities and industry's awareness of the threat of *B. cepacia* to drug manufacturers leading to a more proactive approach to product testing and process control. Some of the enforcement reports contained the following statement "as a precautionary measure due to potential risk of product contamination with the bacteria *B. cepacia*" (Table 2). That statement does not clarify why the assessment was concluding there was a potential risk of product contamination. Based upon that statement it can be inferred that product testing might have been negative and that *B. cepacia* was possibly detected in water samples or during environmental monitoring. Contaminated drugs ranged from decongestants, antihemetics, nasal drops, acetaminophen syrups, antihistamines, hand sanitizers, opioids, antifungals, laxatives, ear drops, phenobarbital oral solutions, antipsychotics, laxatives, suppositories, etc. (Table 2). Other *Burkholderia* species contaminated several products (Table 2). Three recalls were due to the presence of *B. gladioli*, *B. multivorans*, and *B. contaminans* (Table 1).

Several recent morbidity and mortality incidents were found to be related to drugs contaminated with *B. cepacia*. An outbreak of *B. cepacia* complex (Bcc) pseudo bacteremia was associated to contaminated antiseptic formulations.[12] *B. cepacia* was isolated from blood cultures of 40 patients and antiseptic formulations. The outbreak investigation determined that the formulation was misused as a skin antiseptic during blood culture. The contaminated product was discarded and the staff retrained. Another outbreak was reported at a private hospital where thirteen cancer patients undergoing chemotherapy developed *B. cepacia* bacteremia due to a contaminated antiemetic drug.[5] Daily aseptic practices and training stopped the outbreak. Opened and unopened vials of the antiemetic drug grew *B. cepacia*.

A recent contamination of an emollient laxative triggered a multistate outbreak of *B. cepacia* infections in the USA.[6] Five states reported more than 53 cases. Furthermore, *B. cepacia* was detected in the water system used for product manufacturing.[7] Becker et al.[8] reported a similar situation in a German hospital where two patients died of a multi-organ failure and had *B. cepacia* isolated from respiratory samples. The contamination was tracked to an octenidine mouthwash and the manufacturing process. Whole genome sequencing and other genotyping methods confirmed the identity of isolates from patients, products, and manufacturing samples.

Table 2. Drug recalls for non-sterile products and raw materials based upon FDA enforcement reports (June 2012-2019) (n=163). Cont'd

Number	Product	Reason for Recall
106	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
107	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
108	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
109	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
110	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
111	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
112	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
113	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
114	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
115	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
116	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
117	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
118	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
1119	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
120	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
121	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
122	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
123	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
124	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
125	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
126	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
127	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
128	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
129	Gaia Kratom (Mitragyna Speciosa) Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
130	Maeng Da Kratom, Packaged in Rram Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
131	White Vein Kratom, Packaged in Rram Powder	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
132	White Vein Kratom, Packaged in Capsules	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
133	Maeng Da Kratom, Packaged in Capsules	Microbal Contamination of Non-Sterile Product; FDA analysis found *Salmonella* contamination.
134	Psyllium Fiber Supplement, 100% Natural Psyllium Fiber Laxative, 100 Capsules Per Bottle	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
135	Fiber Capsules for Regularity, Dietary Fiber Supplement	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
136	Equate Fiber Therapy, 100% Natural Psyllium Husk Fiber, Fiber Laxative/Fiber Supplement, Capsules	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
137	Leader Fiber Capsules, 100% Natural Psyllium Fiber Laxative, Dietary Fiber Supplement,	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
138	Up&Up Psyllium Fiber Supplement, 100% Natural Psyllium Husk, Fiber Therapy for Regularity/Fiber Supplement, Capsules	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
139	Wal-Mucil 100% Natural Fiber, 100% Natural Psyllium Seed Husk, Fiber Laxative/Supplement, Capsules	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
140	Wal-Mucil Plus Calcium Fiber Capsules,100% Natural Fiber, 100% Natural Psyllium Seed Husk, Calcium/Dietary Fiber Supplement, Capsules	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
141	Fiber Capsules, Fiber Laxative/Fiber Supplement, 100% Natural Psyllium Fiber.	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
142	Simply Right Healthcare Fiber Capsules, 100% Natural Psyllium Fiber, Fiber Supplement, Fiber Laxative for Regularity	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
143	Premier Value Fiber Capsules, Fiber Capsules, 100% Natural Psyllium Fiber, Relieves Constipation, Restores Regularity	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
144	Premier Value Fiber Plus Calcium Supplement Capsules,	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
145	Fiber Capsules, 25 capsules per bottle, Psyllium Husk Fiber	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.

Table 2. Drug recalls for non-sterile products and raw materials based upon FDA enforcement reports (June 2012-2019) (n=163). Cont'd

Number	Product	Reason for Recall
146	Limed Bone Gelatin, Packaged in Six 125 kg Fiber Drums	Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material.
147	Lemon Verbena Hand Sanitizer Spray, Alcohol Free, Active Ingredient Benzalkonium Chloride 0.1%	Microbial Contamination of Non-Sterile Products: Elevated counts of bacteria was found, *Serratia liquefaciens*.
148	Lavender Hand Sanitizer Spray, Alcohol Free, Active Ingredient Benzalkonium Chloride 0.1%	Microbial Contamination of Non-Sterile Products: Elevated counts of bacteria was found, *Serratia liquefaciens*.
149	Ocean Hand Sanitizer Spray, Alcohol Free, Active Ingredient Benzalkonium Chloride 0.1%	Microbial Contamination of Non-Sterile Products: Elevated counts of bacteria was found, *Serratia liquefaciens*.
150	Ocean Hand Sanitizer Spray, Alcohol Free, Active Ingredient Benzalkonium Chloride 0.1%	Microbial Contamination of Non-Sterile Products: Elevated counts of bacteria was found, *Serratia liquefaciens*.
151	Pomegranate Hand Sanitizer Spray, Alcohol Free, Active Ingredient Benzalkonium Chloride 0.1%	Microbial Contamination of Non-Sterile Products: Elevated counts of bacteria was found, *Serratia liquefaciens*.
152	Ginger Lime Hand Sanitizer Spray, Alcohol Free, Active Ingredient Benzalkonium Chloride 0.1%	Microbial Contamination of Non-Sterile Products: Elevated counts of bacteria was found, *Serratia liquefaciens*.
153	Medicated Better Braids, La Laque (salicylic acid) Spray, 2%	Microbial Contamination of a Non-Sterile Products: The product had a positive *Staphylococcus aureus* test result.
154	DERMATONE (Titanium Oxide 6% and Zinc Oxide 4.7%) No-Touch Sunscreen Stick, SPF 50	Microbial Contamination of a Non-Sterile Products: The product had a positive *Staphylococcus aureus* test result.
155	Regular Strength Antacid Liquid (Alumina/Magnesia/Simethicone/ Antacid & Anti Gas); Mint	Microbial Contamination of Non-Sterile Products: Lot in question had an elevated microbial count outside of specifications and *E. coli* contamination.
156	Entertainer's Secret Throat Relief, 2.0 FL oz (59.2 mL), Honey Apple Flavor	Microbial Contamination of Non-Sterile Products: Lot in question had an elevated microbial count outside of specifications and *E. coli* contamination.
157	Sinus Relief (Oxymetazoline HCl) Nasal Decongestant, 0.05%	Microbial Contamination of Non-Sterile Products: Failed microbiological testing for *Pseudomonas aeruginosa*.
158	Germ Bloc Health Hand Sanitizer Foam (Benzalkonium Chloride 0.13%)	Microbial Contamination of Non-Sterile Products: Failed microbiological testing for *Pseudomonas aeruginosa*.
159	Ranitidine Hydrochloride Tablets, USP, 150 mg, OTC, a) Equate Brand Maximum Strength Acid Reducer, b)Equaline Brand Maximum Strength Heartburn Relief	Microbial Contamination of Non-Sterile Products: A lot of raw material used in the manufacture of Ranitidine was positive for *Pseudomonas* sp.
160	Eco-Dent Sparkling Clean Mint Ultimate Essential MouthCare, Natural Daily Rinse and Oral Wound Cleanser/Oral Debriding Agent, 8 fl oz (237 mL) Bottle, Alcohol Free	Microbial Contamination of Non-Sterile Products; Product was found to be contaminated with *Sphingomonas paucimobilis* bacteria.
161	REEVA (Triclosan) Antibacterial Hand Soap and Dishwashing Liquid, Green Apple, 0.10%, 24 fl oz. Bottle	Microbial Contamination of a Non-Sterile Products: Product was found to be contaminated with the bacteria, *Sarcina lutea*.
162	SyrSpend SF Suspending Base	Microbial contamination of Non-Sterile Product; product contamination with yeast and mold (*Paecilomyces saturatus* and *Aspergillus fumigatus*).
163	Magnesium Citrate Oral Solution, Packaged in (296 mL) Glass Bottle, OTC, Labeled as: a) GoodSense Magnesium Citrate Oral Solution Saline Laxative Very Low Sodiumb) Premier Value Magnesium Citrate Oral Solution Saline Laxative Very Low Sodium, c) Swan Very Low Sodium Citroma Magnesium Citrate, NDC 0869-686-38, d) Magnesium Citrate Oral Solution Saline Laxative Low Sodium	Microbial contamination of non-sterile products: product was found to contain mold, identified as *Rhinocladiella similis*.

Table 3. Drug recalls by *B. cepacia* contamination from June 2012-June 2019.

Year	Recalls
2012	6
2013	0
2014	0
2015	0
2016	11
2017	25
2018	4
2019	56

Water, the most common raw material in pharmaceutical manufacturing, is also a major source of contamination and accounted for fifteen recalls of non-sterile products (Figure 1). Unfortunately, none of the recalls listed the genus or species detected only citing a high total

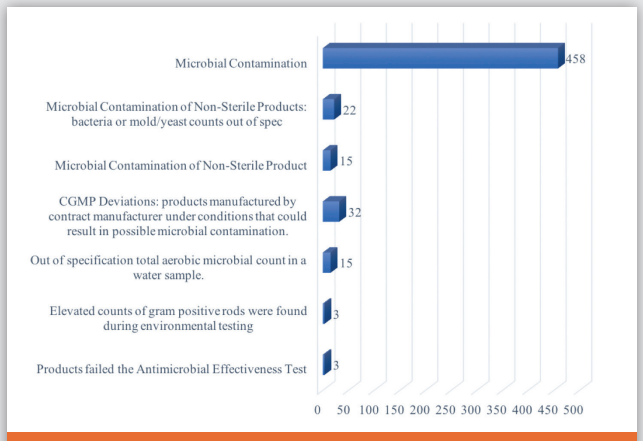

Figure 1. Reasons for non-sterile drug recalls with no microbial identification (n=548) (June 2012-2019).

microbial count. Water system validation is important to minimize bioburden excursions.[13] *B. cepacia* is capable of colonizing surfaces under flowing conditions. The sanitization of the water system by heat or chemical treatment prevents microbial colonization of water lines and biofilm formation.

The persistence of *B. cepacia* in pharmaceutical products is due to the lack of proper cGMP and the use of compendial methods that do not provide the sensitivity and resolution to detect *B. cepacia* in pharmaceutical water, raw materials, and finished products.[5,7,8,10,11] Cundell[13] discussed the risk mitigation steps to exclude *B. cepacia* from non-sterile products and revealed that a proposed and timely USP test for *B. cepacia* was published in the September-October issue of the Pharmacopeia Forum. Some of the steps discussed by Cundell[13] were:

Pharmaceutical ingredients selection

- Product formulation including robust antimicrobial preservative system
- Management of pharmaceutical water systems
- Equipment cleaning and sanitization
- Manufacturing processes
- Risk-based microbial testing programs

Industrial operators and compendial methods severely underestimated *B. cepacia* complex (Bcc) genetic and metabolic diversity. The genome consists of more than one chromosome containing a wide variety of genes, which appeared to be acquired by horizontal transfer.[14] These genes provide resistant to antibiotics, biocides, and adaptation to environmental stresses.[14-17] For instance, the Bcc showed intrinsic antibiotic resistance by the release of beta-lactamases, specific efflux pumps, and the impermeability of the outer membrane to antimicrobial agents. Vigorous biofilm formation is another adaptation providing resistance to antimicrobial treatments.

B. cepacia is also capable of growing on nitro aromatic and aromatic compounds by the action of different enzymes such as monooxygenases (MO) and dioxygenases (DO). These enzymes also oxidize halogenated compounds. Nitro aromatic compounds are major components of many drugs. For instance, antipsychotic and analgesic drugs are based upon chemical structures sensitive to degradation attacks by MO and DO.

Furthermore, the Bcc is currently comprised of approximately 22 species, which are phenotypically similar.[18] However, PCR based methods, pulse field gel electrophoresis (PFE), multilocus sequence typing (MLST) and whole-genome sequencing have been used to accurately identify or detect isolates from different outbreaks and contaminated products.[6,7,19-21]

FDA guidance has been clear and proactive regarding *B. cepacia* contamination.[22] An article published by The Center for Drug Evaluation and Research (CDER) discussed several recall reports and inspection documents regarding points of origin for contamination and anomalies in test methods. The article also discussed the issue of objectionable microorganisms and whether *B. cepacia* can be included in a compendial chapter. Based upon that article, potential causes for product contamination and system breakdown were:

- Inadequate cleaning procedures
- Use of unsuitable grade of water (use of potable water to clean equipment)
- Poor water system controls
- Poor water system design
- Inadequate testing and specifications
- Inadequate manufacturing procedures
- Inadequate validation or lack of environmental monitoring in critical areas

The second most common microorganism detected in non-sterile products, *Ralstonia pickettii*, a Gram-negative bacterial species, was always isolated with *B. cepacia* (Table 2). *R. pickettii* contaminated 45 drugs (Table 1). *R. pickettii* was not detected in any recalls in 2004-2011 (Table 1). However, two non-sterile drugs were recalled in 1995-2006.

Mold Contamination of Pharmaceutical Products

Analysis of enforcement reports indicated that 52 recalls cited yeast and/or mold contamination but only six recalls listed genera or species (Table 4). Of these recalls, 27 citations were for sterile and 25 for non-sterile drugs. Yeast and/or mold recalls for non-sterile drugs were lower than in 1995-2006 when 31 citations were reported.[10] However, the numbers were higher than in 2004-2011. Enforcement data from 2004-2011 showed 23 recalls due to yeast and mold contamination.[11] Back in 1998-2006, mold contaminated only six sterile drugs.[10]

Aspergillus fumigatus and *Paecilomyces saturatus* simultaneously contaminated a non-sterile product while *Aspergillus* spp. contaminated four different sterile formulations (Table 4). One more recall from a non-sterile drug cited *Rhinocladiella similis* as the contamination source. Yeast was detected in nine recalls simultaneously with *B. cepacia* but no identification was provided (Table 4). Yeast and mold previously isolated from contaminated products were the following: *Acremonium* spp., *Aspergillus* spp., *Penicillium* spp., *Aspergillus sidowii*, *Aspergillus niger*, *Candida lipolytica*, and *Candida parapsilosis*.[10,11] Of all these, only *Aspergillus* spp. was found again in four samples of sterile products for the years 2012-2019 (Table 1).

The lack of identification of mold and yeast contamination is a worrisome trend in the pharmaceutical industry with major implications to determine proper corrective actions and process control optimization.[23,24] Cundell[23] previously stated the poor job performed by the pharmaceutical industry in the area of mycology. This statement is further confirmed by current recall data where only 12% of recalls showed proper identification (Table 4). Previous studies reported similar practices with only 10% and 17% of recalls showing either genus or species information.[10,11] However, when sterile products were contaminated by mold, 33% showed identification at the genus level.[10] Identification of yeast and mold isolates provides

Table 4. Drugs recalled by mold and yeast contamination (n=52) (June 2012-2019).		
Number	**Product**	**Reason for Recall**
1	Lactated Ringer's and 5% Dextrose Injection	Non-Sterility: One confirmed customer report that product contained spore-like particulates, consistent with mold.
2	Lactated Ringer's and 5% Dextrose Injection	Non-Sterility: Confirmed customer complaint of product contaminated with mold.
3	Magnesium Sulfate 2 grams in Dextrose 5% for Injection,	Non-Sterility; mold contamination.
4	Carboxymethylcellulose Sodium 0.5% Ophthalmic Solution	Non-Sterility: Customer complaints of mold in the product after use and handling due to the fact that the preservative used in the lots of Carboxymethylcellulose Sodium 0.5% Ophthalmic Solution may not be effective through expiry.
5	Dextrose Vial in Sterile Water	Non-Sterility: 50% dextrose is being recalled after particulate matter, later identified as mold, was found floating in the product.
6	Peritoneal Dialysis Solution	Non-Sterility: Complaints of leaks and particulate matter identified as mold in the solution bag and the overpouch.
7	Ascorbic Acid Sterile Injection	Non-Sterility: mold contamination.
8	Lactated Ringers and 5% Dextrose Injection	Non-Sterility: Confirmed customer complaint of particulate matter floating within the solution of the primary container, consistent with mold.
9	Lactated Ringer Irrigation	Non-Sterility: Confirmed customer report of dark, fibrous particulates floating within the solution of the primary container, which were subsequently identified as mold.
10	Human Chorionic Gonadotropin, in 0.5 ml Syringe	Non-sterility: presence of mold confirmed by outside laboratory at the 14-day culture.
11	Linezolid Injection	Presence of Particulate Matter; white particulate matter identified as mold was found in one bag
12	Levofloxacin in 5% Dextrose Injection	Presence of Particulate Matter; contains visible particulate matter identified as mold.
13	Natural SPF 28 Sunscreen,	Microbial Contamination of Non-Sterile Product; mold.
14	Amoxicillin for Oral Suspension	Microbial Contamination of Non-Sterile Products: Suspensions made from these lots of Amoxicillin 125 mg/5 mL showed yeast and mold growth at the 14-day time point.
15	All Compounded Products, Packaged in Plastic Infusion Bags, Devices, Syringes and Glass Vials	Lack of Assurance of Sterility; potential for mold contamination.
16	Dicopanol FusePaq Kit for Oral Suspension	Microbial Contamination of Non-Sterile Products: Fusion Pharmaceuticals is recalling the Dicopanol FusePaq Kit due to Total Yeasts and Molds Count above USP limits.
17	Norepinephrine Sodium Chloride, For IV Use Only	Lack of Assurance of Sterility: A mold like substance was discovered on the surface of an unopened bag of Sodium Chloride 0.9% while prepping the bag for production.
18	Phytobase Cream, Prescription Compounding Natural Self-emulsifying Oil-in Water Vehicle for Oil-solvents Ingredients. Contains Phytosomes (Plant Oil Bodies)	Microbial Contamination of Non-Sterile Products: recalling six lots due to the presence of mold.
19	Pentravan Base. For Prescription Compounding, Oil-in-Water Emulsion, PLO Gel Alternative, Preserved and Fragrance-Free	Microbial Contamination of Non-Sterile Products: recalling six lots due to the presence of mold.
20	Pentravan Plus Base For Prescription Compounding, Oil-in-Water Emulsion Base Alternative to PLO gel, Added Emulsifier Ad Viscosity-enhancing Agent for Use with High Concentrations of Active Ingredients. Preserved and Fragrance-free	Microbial Contamination of Non-Sterile Products: recalling six lots due to the presence of mold.
21	0.9% Sodium Chloride Injection	Lack of Assurance of Sterility; complaints of mold in the overpouch.
22	0.9% Sodium Chloride Injection	Lack of Assurance of Sterility: Recalling firm reported a complaint for mold on the interior surface of the overpouch.
23	Clindamycin Phosphate and Benzoyl Peroxide Gel	Microbial Contamination of Non-Sterile Product; small number of tubes may include the presence of mold on the cap.

valuable information to determine the root cause of system failure and lack of process control.

Mycological expertise by either in-house resources or contract testing laboratories must be a basic part of the environmental and quality control program. It is inexcusable to neglect this important area of process control since molds outcompete bacteria at lower water activity environments.[23] Accurate mold identification is based upon the amplification and sequencing of internal transcribed spacer (ITS) regions located between the small and large-subunits of the ribosomal gene.[23] Specific PCR assays targeted different mold species in pharmaceutical products.[24] Major outbreaks of fungal meningitis and endophthalmitis were associated to contamination of injectable and ocular drugs during manufacturing.[25,26] Some of the mold isolates were normal flora in cleanroom environments, which evidently by the lack of process control and cGMP practices led to unfortunate events of morbidity and mortality.[25-27]

Unidentified Microbial Contamination of Non-Sterile Products

Of 713 non-sterile recalls, 548 (77%) did not provide any information on the microorganisms responsible for the contamination. The reports did not have any genus or species level identification. This number was higher than the one reported for non-sterile drugs in 1995-2006, e.g.,

Table 4. Drugs recalled by mold and yeast contamination (n=52) (June 2012-2019). Cont'd		
Number	**Product**	**Reason for Recall**
24	Lactulose Solution	Microbial contamination of non-sterile product: product failed Total Yeast/Mold Count specification.
25	Lactulose Solution	Microbial contamination of non-sterile product: product failed Total Yeast/Mold Count specification.
26	Magnesium Citrate Oral Solution a) Magnesium Citrate Oral Solution Saline Laxative Very Low Sodium, b) Magnesium Citrate Oral Solution saline laxative very low sodium, c) Very Low Sodium Citroma Magnesium Citrate, Magnesium Citrate Oral Solution Saline Laxative Low Sodium	Microbial contamination of non-sterile products: product was found to contain mold, identified as *Rhinocladiella similis*.
27	SF Suspending Base	Microbial contamination of Non-Sterile Product; product contamination with yeast and mold (*Paecilomyces saturatus* and *Aspergillus fumigatus*).
28	Linezolid Injection	Lack of Assurance of Sterility; confirmed customer report of a leaking bags and mold found between the outer bag and the overwrap.
29	Levofloxacin in 5% Dextrose Injection	Lack of Assurance of Sterility; confirmed customer report of a leaking bags and mold found between the outer bag and the overwrap.
30	Levetiracetam in 0.82% Sodium Chloride Injection	Lack of Assurance of Sterility; confirmed customer report of a leaking bags and mold found between the outer bag and the overwrap.
31	Levetiracetam in 0.75% Sodium Chloride Injection	Lack of Assurance of Sterility; confirmed customer report of a leaking bags and mold found between the outer bag and the overwrap.
32	Levetiracetam in 0.54% Sodium Chloride Injection	Lack of Assurance of Sterility; confirmed customer report of a leaking bags and mold found between the outer bag and the overwrap.
33	Levofloxacin in 5% Dextrose Injection	Lack of Assurance of Sterility; confirmed customer report of a leaking bags and mold found between the outer bag and the overwrap.
34	Levofloxacin in 5% Dextrose Injection	Lack of Assurance of Sterility; confirmed customer report of a leaking bags and mold found between the outer bag and the overwrap.
35	Natural dream cream, Shea Butter and Mint	Microbial Contamination of Non-Sterile Products: Consumer complaint and subsequent testing found lot to be out of specification for mold.
36	Sodium Tablets, 10 mg	Chemical Contamination: The recall has been initiated based on multiple complaints received from pharmacists and consumers reporting that they detected an off-odor, described as moldy, musty or fishy in nature which has been identified as trace levels of Tribromoanisole (TBA) and Trichloroanisole (TCA).
37	Gabapentin Tablets	Chemical Contamination: Gabapentin Sodium tablets is recalled due to complaints related to an off - odor described as moldy, musty or fishy in nature.
38	Pravastatin Sodium Tablets	Chemical Contamination: Pravastatin Sodium Tablets isbeing recalled due to complaints related to an off-odor described as moldy, musty or fishy in nature.
39	Topiramate Tablets	Chemical Contamination: Topiramate Tablets is being recalled due to complaints related to an off - odor. described as moldy, musty or fishy in nature.
40	Pediatric Cardioplegia	Non-Sterility; microbial contamination identified as *Aspergillus* species.
41	Cardioplegia with Lidocaine	Non-Sterility; microbial contamination identified as *Aspergillus* species.
42	Adenosine 90 mg in 0.9% Sodium Chloride	Non-Sterility; microbial contamination identified as *Aspergillus* species.
43	LOW Potassium Cardioplegia	Non-Sterility; microbial contamination identified as *Aspergillus* species.
44	Liquid, Docusate Sodium Stool Softener Laxative	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination.
45	Syrup, Docusate Sodium, Stool Softener Laxative	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination.
46	Syrup Natural Vegetable Laxative, Sennoside	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination.
47	Chlorpheniramine Maleate Syrup	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination.
48	Liquid Natural Vegetable Stimulant	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination.
49	Liquid, Docusate Sodium, Stool Softener Laxative	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination.
50	Syrup, Docusate Sodium, Stool Softener Laxative	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination.
51	Liquid Natural Vegetable Stimulant	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination.
52	Chlorpheniramine Maleate Syrup	Microbial contamination of Non-Sterile Products; presence of yeast and potential *B. cepacia* contamination.

43%.[10] Sutton and Jimenez[11] reported 28% of recalls without microbial identification in 2004-2011.[11]

Figure 1 shows the different reasons cited for non-sterile drug recalls. Since non-sterile drug testing looks for bioburden levels and objectionable microorganisms, it was very difficult to ascertain whether recalls were due to high levels of contamination or the presence of pathogenic microorganisms. Microbial contamination (458 recalls) was the primary reason to retrieve products from the market. The other reasons were:

- cGMP Deviations: products manufactured by contract manufacturer under conditions that could result in possible microbial contamination (32 recalls)

- Microbial Contamination of Non-Sterile Product (15 recalls)
- Microbial Contamination of Non-Sterile Products: bacteria or mold/yeast counts out of specification (22 recalls)
- Out of specification total aerobic microbial count in a water sample (15 recalls)
- Elevated counts of Gram-positive rods were found during environmental testing (3 recalls)
- Products failed the Antimicrobial Effectiveness Test (3 recalls)

Lacking information on the microbial contaminant did not help to determine the root cause of the problem and establish proper remedial actions. Because non-sterile pharmaceuticals are allowed to have a microbial bioburden, it is critical to have a good rationale to determine what is an objectionable microorganism and the risk to consumers and manufacturing processes. Accurate microbial identification is critical to understand process control deviations and contamination excursions.[28] It is indefensible not to have a proper microbial identification program with standard operating procedures (SOP's) including analyst training. Analysts should be knowledgeable on basic microbiological procedures such as macroscopic features, e.g., looking at the plates with the naked eye to recognize whether the growth is bacterial or fungi, microscopic features, e.g., Gram-staining, spore staining, and simple biochemical tests such as catalase testing, oxidase testing, and substrate utilization tests. Ribosomal 16S rRNA gene sequencing is the current standard for bacterial identification.[28] The 16S ribosomal gene codes for the RNA component of the 30S subunit of the bacterial ribosome. They are essential genes which are highly conserved. Large publicly available databases containing 16S rRNA gene sequences provide enough phylogenetic information to identify bacteria at the genus and species level.

How would you know if a given microbial isolate is objectionable if you do not perform an identification? The products are non-sterile and they can have a microbial load that might not be objectionable.[11] Different technologies and procedures are available that rely on phenotypic and genotypic identification which provide the information necessary to determine the nature of the microorganisms present in a given sample.[28,29] Sandle[4] published an excellent review on the topic of microbial identification strategies in the pharmaceutical industry. However, based upon recall data some companies are still struggling to understand the risk of not having a functional microbial identification program.

Microbial Contamination of Sterile Products by Non-Sterility

When sterile drugs were recalled for non-sterility, four out of 95 recalls were due to *Aspergillus* species and one recall for the following bacterial species: *Bacillus thuringiensis*, *Bacillus circulans*, *Variovorax paradoxus*, *Herbaspirillum huttiense*, *Achromobacter xylosoxidans*, *Sphingomonas paucimobilis*, *Klebsiella pneumoniae*, and *Staphylococcus warneri* (Table 1, Figure 2). Of the cited eight bacterial species, three were Gram-positive and five were Gram-negative. The

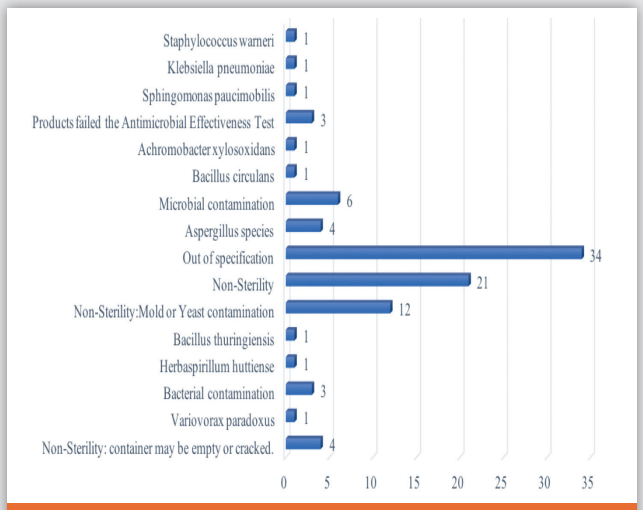

Figure 2. Reasons for sterile drug recalls due to non-sterility (n=95) (June 2012-2019).

presence of Gram-negative bacteria in sterile products might indicate a possible problem with the water system during manufacturing while Gram-positive bacteria such as *Bacillus* and *Staphylococcus* can be the result of improper environmental control systems.[4,10] The diversity of bacterial species contaminating sterile drugs in 1998-2006 was completely different with *B. cepacia* (five recalls), *P. aeruginosa* (one recall), *Methylobacterium* spp. (three recalls), *Mycobacterium chlelonae* (three recalls), *Stenotrophomonas maltophilia* (one recall), *Ralstonia pickettii* (one recall), *Serratia* spp. (one recall) and *Bacillus licheniformis* (one recall). None of these bacterial species contaminated sterile drugs in 2012-2019.

Out of specification, (OOS) results were the most cited violations with 34 followed by non-sterility (21 recalls) and mold and yeast contamination (twelve recalls) (Figure 2). Bacterial contamination, microbial contamination, failed antimicrobial effectiveness test, and container problems were the other reasons for non-sterility recalls. However, 87% of recalls did not have microbial identification. This was very similar to the numbers reported by Jimenez,[10] e.g., 88%.

What was the contamination source? Was it bacteria, mold, or both? Accurate investigation of OOS incidents and proper implementation of corrective actions required information that was not available from the enforcement reports. How do companies optimize microbial contamination control for sterile products if they do not identify the microorganism causing the excursion? Compendial sterility testing of pharmaceutical drugs is based upon the addition of aliquots or membranes with the concentrated samples to different types of media.[30] One of the media is specific for aerobic microorganisms and the other selectively enriches for anaerobic microorganisms. The standard incubation time for both media is fourteen days. Different temperatures are used for aerobic, 25°C, and anaerobic microorganisms, 35°C. Turbidity in the enrichment media indicates positive microbial growth. The test is cumbersome and requires special gowning procedures, equipment, and laboratory facilities to

reduce the risk of analyst's and environmental contamination during testing. Sample incubation after testing requires specific incubators and daily visual readings of the enrichment cultures by the analyst to document the results. Visual readings are extremely subjective; when slow microbial growth is present, a slight pellicle can form at the bottom of the test tube or canister and will not be seen unless the sample is moderately shaken. Furthermore, in some cases when the enrichments are turbid upon the addition of samples, it is very hard to ascertain the presence or absence of microbial growth after incubation. Therefore, samples must be streaked onto solid agar media to determine the presence of any viable and culturable microorganism. This additional step extends the completion time for the test. Different technologies have been reported for rapid testing of sterile pharmaceutical products.[31-34] Previous studies reported the feasibility of ATP bioluminescence and PCR analysis using universal bacterial sequences for testing of liquid products. Other studies demonstrated the evaluation of solid phase laser scanning cytometry and colorimetric sensors with reflected light to determine the amount of released carbon dioxide (CO_2). Regardless of the test used, identification of the microbial contaminant will provide valuable information to complete the OOS investigation.[28,35] FDA guidance to aseptic manufacturing has been quite clear stating the need to identify microorganisms when present in products and aseptic processing at the genus and species level preferably with genotypic tests.[35]

Lack of Sterility Assurance

Based upon enforcement report data, LSA was again the number one reason for sterile drugs recalls in 2012-2019. Table 5 shows only 100 out of 1056 recalls. The drugs recalled ranged from injectable saline solutions, hormones, ophthalmic solutions, water for injection, antibiotics, vitamins, anesthetics, amino acids solutions, pain relievers, opioid analgesics, narcotics, vasopressors, etc.

Table 6 shows the different reasons for 1056 LSA citations. The number one reason cited was undetermined cGMP issues (184 recalls) followed

Table 5. Sterile drugs cited due to lack of sterility assurance (June 2012-2019) (n=1056). Only 100 recalls are shown.

Number	Product	Reason
1	HCG (Lyophilized)	Lack of Assurance of Sterility: The recall is being initiated due to a lack of sterility assurance and concerns associated with the quality control processes identified during an FDA inspection.
2	Sermorelin/GHR	Lack of Assurance of Sterility: The recall is being initiated due to a lack of sterility assurance and concerns associated with the quality control processes identified during an FDA inspection.
3	Lubrisine eye drops (polyethylene glycol 400 0.4% and Propylene Glycol 0.3%)	Lack of Sterility Assurance and Incorrect/Undeclared excipient: Product was found to contain undeclared colloidal silver
4	Acetylcysteine Ophthalmic Solution	Lack of Assurance of Sterility; FDA inspectional findings resulted in concerns associated with quality control procedures that impacted sterility assurance
5	Alprostadil IN NS Injection	Lack of Assurance of Sterility; FDA inspectional findings resulted in concerns associated with quality control procedures that impacted sterility assurance
6	Atropine Injection	Lack of Assurance of Sterility; FDA inspectional findings resulted in concerns associated with quality control procedures that impacted sterility assurance
7	Acetylcysteine Injection	Lack of Assurance of Sterility: all sterile products compounded, repackaged, and distributed by this compounding pharmacy due to lack of sterility assurance and concerns associated with the quality control processes.
8	Amikacin Injection	Lack of Assurance of Sterility: all sterile products compounded, repackaged, and distributed by this compounding pharmacy due to lack of sterility assurance and concerns associated with the quality control processes.
9	Methylprednisolone Acetate injectable Balanced Solutions	Lack of Assurance of Sterility: All sterile products compounded, repackaged, and distributed by this compounding pharmacy due to lack of sterility assurance and concerns associated with the quality control processes.
10	Bacteriostatic Water for Injection 0.9% Injectable	Lack of Assurance of Sterility: All sterile products compounded, repackaged, and distributed by this compounding pharmacy due to lack of sterility assurance and concerns associated with the quality control processes.
11	Cyclosporin in Corn Oil Injectable Balanced Solutions	Lack of Assurance of Sterility: All sterile products compounded, repackaged, and distributed by this compounding pharmacy due to lack of sterility assurance and concerns associated with the quality control processes.
12	AmBisome (amphotericin B) liposome for Injection	Lack of Sterility Assurance; During a routine simulation of the manufacturing of AmBisome, a bacterial contamination was detected in some media fill units. No contaminated batches have actually been identified in the finished product, but there is a possibility of contamination.
13	Ascorbic Acid (Non-corn Source) 500 mg/mL Injectable	Lack of Assurance of Sterility; FDA inspectional findings resulted in concerns associated with quality control procedures that impacted sterility assurance
14	Dextrose PF 50% Injectable	Lack of Assurance of Sterility; FDA inspectional findings resulted in concerns associated with quality control procedures that impacted sterility assurance
15	Testosterone Cypionate 100 mg/mL, 200 mg/mL, 20 mg/mL Oil Injectable	Lack of Assurance of Sterility; FDA inspectional findings resulted in concerns associated with quality control procedures that impacted sterility assurance
16	Vitamin D 50,000 I.U./mL Injectable	Lack of Assurance of Sterility; FDA inspectional findings resulted in concerns associated with quality control procedures that impacted sterility assurance
17	Vancomycin PF (BSS) 1%	Lack of Assurance of Sterility: Recalling bevacizumab and vancomycin due to concerns of sterility assurance with the specialty pharmacy's independent testing laboratory.

Table 5. Sterile drugs cited due to lack of sterility assurance (June 2012-2019) (n=1056). Only 100 recalls are shown. Cont'd		
Number	**Product**	**Reason**
18	Lidocaine 4% Urethral Gel	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
19	Gentamycin 80mg/1000cc 0.9% NS	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
20	Oxytocin 30 Units in 500mL Sodium Chloride 0.9%	Lack of Assurance of Sterility: The firm expanded the recall to other injectable products due to lack of assurance of sterility from poor aseptic practices observed at the firm.
21	Polidocanol 0.5% Solution for Injection	Lack of Assurance of Sterility: Lack of sterility assurance in compounded aseptically filled injectable products.
22	Chlorhexidine Gluconate 0.02% Opthalmic Solution	Lack of Assurance of Sterility: A voluntary recall of all compounded sterile preparations within expiry. The recall is being initiated in connection with a recent FDA inspection due to observations associated with certain quality control procedures that present a risk to sterility assurance.
23	Chorionic Gonadotropin/Mannitol 10000 U/0.1 gm Powder Packaged in a WhiteJar	Lack of Assurance of Sterility: A voluntary recall of all compounded sterile preparations within expiry. The recall is being initiated in connection with a recent FDA inspection due to observations associated with certain quality control procedures that present a risk to sterility assurance.
24	Dexamethasone Sodium Phosphate 4 mg/mL Injectable	Lack of Assurance of Sterility: A voluntary recall of all compounded sterile preparations within expiry. The recall is being initiated in connection with a recent FDA inspection due to observations associated with certain quality control procedures that present a risk to sterility assurance.
25	Fentanyl Injectable 6000 mcg/mL Packaged in 30 mLor 60 mL Syringes	Lack of Assurance of Sterility: A voluntary recall of all compounded sterile preparations within expiry. The recall is being initiated in connection with a recent FDA inspection due to observations associated with certain quality control procedures that present a risk to sterility assurance.
26	Lidocaine 1% Injectable Packaged in an Amber Glass Injectable Vial	Lack of Assurance of Sterility: A voluntary recall of all compounded sterile preparations within expiry. The recall is being initiated in connection with a recent FDA inspection due to observations associated with certain quality control procedures that present a risk to sterility assurance.
27	Opthalmic Ointment Base Ointment Packaged in a White Ointment Tube	Lack of Assurance of Sterility: A voluntary recall of all compounded sterile preparations within expiry. The recall is being initiated in connection with a recent FDA inspection due to observations associated with certain quality control procedures that present a risk to sterility assurance.
28	Paraben Water for Injection Packaged in a Sterile 1000 mL Clear Bottle	Lack of Assurance of Sterility: A voluntary recall of all compounded sterile preparations within expiry. The recall is being initiated in connection with a recent FDA inspection due to observations associated with certain quality control procedures that present a risk to sterility assurance.
29	Prednisolone Acetate 50 mg/mL Injectable Packaged in an Amber Glass Injectable Vial	Lack of Assurance of Sterility: A voluntary recall of all compounded sterile preparations within expiry. The recall is being initiated in connection with a recent FDA inspection due to observations associated with certain quality control procedures that present a risk to sterility assurance.
30	ALPROSTADIL, 10 mcg/mL, Injectable	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
31	AVASTIN, 1.25mg/0.5mL, injectable, 0.05 mL Plastic Syringe	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
32	TOBRAMYCIN, 480mg/1000 mL, Solution for Irrigation	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection
33	Leuprolide 50 mcg/0.1 mL Micro Lupron Kit	Lack of sterility assurance; All lots of sterile products compounded by the pharmacy that are within expiry were recalled due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
34	Liposomal Amphotericin B 130 mg in Dextrose Bags	Lack of sterility assurance.
35	Ceftazidime Various Strength in Normal Saline Bags	Lack of sterility assurance.
36	Cefazolin Various Strengths in Normal Saline Bags	Lack of sterility assurance.
37	Linezolid Various Strengths in Dextrose	Lack of sterility assurance.
38	Immune Globulin G Human Various Strengths	Lack of sterility assurance.
39	Nystatin 50,000 Units Suppository	Lack of Assurance of Sterility and Stability Data does not Support Expiry: recent inspection observations associated with certain quality control procedures that present a risk to sterility and quality assurance.
40	Dexamethasone Sodium Phosphate PF (10 mg/mL)	Lack of Assurance of Sterility; The firm is recalling all sterile preparations that are within expiry due to deficient practices, which may have an impact on sterility assurance.
41	Phenylephrine 1.5%/ Lidocaine 1%, 1 mL Single Use Vial, For Intracameral Injection	Lack of Assurance of Sterility; The firm is recalling all sterile preparations that are within expiry due to deficient practices, which may have an impact on sterility assurance.
42	Methylcobalamin 5000 mcg/mL Preservative Free Injection	Lack of Assurance of Sterility: A recall of all compounded sterile preparations within expiry is being initiated due to observations associated with poor sterile production practices resulting in a lack of sterility assurance for their finished drugs.
43	Progesterone 100 mg/mL Ethyl Oleate Injection	Lack of Assurance of Sterility: A recall of all compounded sterile preparations within expiry is being initiated due to observations associated with poor sterile production practices resulting in a lack of sterility assurance for their finished drugs.

Table 5. Sterile drugs cited due to lack of sterility assurance (June 2012-2019) (n=1056). Only 100 recalls are shown. Cont'd		
Number	**Product**	**Reason**
44	Papaverine Phentolamine Prostaglandin	Lack of Assurance of Sterility: Firm is recalling all unexpired lots of sterile compounded products after FDA inspection found concerns of lack of sterility assurance.
45	Ephedrine Sulfate in 0.9% Sodium Chloride 5 mL, 25 mg/5 mL (5 mg/mL) Single-Dose Syringe	Lack of Sterility Assurance.
46	Sterile Eyewash (Sterile Isotonic Phosphate Buffered Saline Solution)	Lack of sterility assurance: leaking containers, which could lead to exposure to infectious agents.
47	Fentanyl 10 mcg in 0.9% Sodium Chloride Injectable Drug	Lack of sterility assurance: Microbial growth detected during a routine simulation of the manufacturing process. No batches of distributed product have been identified as actually containing microorganisms.
48	Omnipaque (iohexol) Injection	Defective Container: vial defect was identified that could potentially impact the container closure and result in a lack of sterility assurance and/or the potential for glass particles.
49	Amino Blend Injection, Ornithine/Arginine/Lysine/Lidocaine	Lack of sterility assurance.
50	0.2% Ropivacaine HCl (Preservative Free) in 0.9 Sodium Chloride	Lack of assurance of sterility: Three lots were released where there was a failure to follow proper testing and investigation procedures. Product may be out of specification (OOS) for endotoxin.
51	Bevacizumab (Avastin) syringe	Lack of Assurance of Sterility: Bacterial contamination found after investigation at contract testing laboratory discovered that OOS/failed results were reported to customers as passing. Hence, the sterility of the products cannot be assured.
52	Murocel (methylcellulose) Lubricant Opthalmic Solution	Lack of Assurance of Sterility: Product was found to be OOS for Antimicrobial Effectiveness testing (AET) at the 12-month stability time point.
53	Volumex (Iodinated I 131 Albumin) Injection	Lack of Assurance of Sterility: environmental monitoring report exceeds limits; therefore, sterility cannot be assured.
54	S-Methylcobalamin 1000 mcg/mL (PF) Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.
55	Fentanyl 10 mcg in 0.9% Sodium Chloride Injectable Drug	Lack of sterility assurance: Microbial growth detected during a routine simulation of the manufacturing process. No batches of distributed product have been identified as actually containing microorganisms.
56	Morphine 50 mg in 0.9% Sodium Chloride 5 mL Injectable Drug	Lack of sterility assurance: Microbial growth detected during a routine simulation of the manufacturing process. No batches of distributed product have been identified as actually containing microorganisms.
57	Oxytocin 30 units in 0.9% Sodium Chloride 500 mL, Injectable Drug	Lack of sterility assurance: Microbial growth detected during a routine simulation of the manufacturing process. No batches of distributed product have been identified as actually containing microorganisms.
58	Succinylcholine chloride 100 mg in 5 mL syringe, Injectable Drug	Lack of sterility assurance: Microbial growth detected during a routine simulation of the manufacturing process. No batches of distributed product have been identified as actually containing microorganisms.
59	Latanoprost Ophthalmic Solution	Lack of Assurance of Sterility: Failed at expiry for Preservative Effectiveness Test (PET), therefore the product may be susceptible to microbial growth before the expiry date.
60	Sulfacetamide Sodium Ophthalmic Solution	Lack of Assurance of Sterility; some lots failed Antimicrobial Effectiveness Testing on stability
61	Testosterone Cypionate for Injection, Contains Testosterone Cypionate 200 mg, Also Contains: Cotton Seed Oil, Benzyl Benzoate, Benzyl Alcohol	Lack of Assurance of Sterility: Lack of sterility assurance in compounded aseptically filled injectable products.
62	Mannitol 5% Solution for Injection, Mannitol 50 mg, Also Contains Sterile Water for Injection, Chlorobutanol	Lack of Assurance of Sterility: Lack of sterility assurance in compounded aseptically filled injectable products.
63	Levocarnitine Solution for Injection, l-Carnitine 50 mg, Also Contains Sterile Water for Injection and Benzyl Alcohol pH Adjusted with HCl, 50 mL	Lack of Assurance of Sterility: Lack of sterility assurance in compounded aseptically filled injectable products.
64	METHYLCOBALAMIN FOR INTRAMUSCULAR OR SUBCUTANEOUS USE ONLY, Methylcobalamin 1000 mcg, Also Contains: Benzyl Alcohol, Sodium Chloride, Water, Hydrochloric Acid, and/or Sodium Hydroxide	Lack of Assurance of Sterility: Lack of sterility assurance in compounded aseptically filled injectable products.
65	Papaverine HCl 30 mg, Phentolamine Mesylate 1 mg, Alprostadil 20 mcg	Lack of Assurance of Sterility: Lack of sterility assurance in compounded aseptically filled injectable products.
66	B-Complex/Adenosine Inj. sol, Adenosine-5-Monophosphate 0.03g, Choline Chloride 0.01g, Cyanocobalamin 0.3mg, Inositol 0.05g, Methionine 0.015g, Levocarnitine 0.1g, Chromic Chloride 0.15g, Lidocaine HCl 0.01g, Pyrodoxine HCl 0.005g	Lack of Assurance of Sterility: Lack of sterility assurance in compounded aseptically filled injectable products.
67	Papaverine HCl 30 mg, Phentolamine Mesylate 2 mg, Alprostadil 40 mcg, a) 5 mL and b) 10 mL	Lack of Assurance of Sterility: Lack of sterility assurance in compounded aseptically filled injectable products.
68	Papaverine HCl 30 mg, Phentolamine Mesylate	Lack of Assurance of Sterility: Lack of sterility assurance in compounded aseptically filled injectable products.
69	Papaverine HCl 30 mg, Phentolamine Mesylate 2 mg, Alprostadil 20 mcg	Lack of Assurance of Sterility: Lack of sterility assurance in compounded aseptically filled injectable products.
70	S-Methylcobalamin 1000 mcg/mL (PF) Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.

Table 5. Sterile drugs cited due to lack of sterility assurance (June 2012-2019) (n=1056). Only 100 recalls are shown. Cont'd		
Number	**Product**	**Reason**
71	S-Chorionic Gonad HCG 1000 U/mL Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.
72	SIH-Testosterone Cyp. 200 mg/mL Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.
73	S-methylcobalamin 25 mg/mL (PF) Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.
74	SIH-Testosterone Cyp. 20 mg/mL Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.
75	SIU-Papaverine 30 mg/mL Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.
76	SIU-Papav/Phent 24/1 mg/mL Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.
77	SIU-Papav/Phentol 30/1 mg/mL Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.
78	SIU-Phent .4 mg/PGE1 20 mcg/mL Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.
79	SIU-Papav/Phent 30/1 mg Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.
80	SIU-Papav/Phentol 30/.5 mg/mL Injection	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced.
81	Sterile Eyewash (Sterile Isotonic Phosphate Buffered Saline Solution)	Lack of sterility assurance: leaking containers, which could lead to exposure to infectious agents.
82	Sterile Eyewash (Sterile Isotonic Phosphate Buffered Saline Solution)	Lack of sterility assurance: leaking containers, which could lead to exposure to infectious agents.
83	Sterile Eyewash (Sterile Isotonic Phosphate Buffered Saline Solution)	Lack of sterility assurance: leaking containers, which could lead to exposure to infectious agents.
84	Sterile Eyewash (Sterile Isotonic Phosphate Buffered Saline Solution)	Lack of sterility assurance: leaking containers, which could lead to exposure to infectious agents.
85	Midazolam HCl in 0.9% Sodium Chloride	Lack of sterility assurance.
86	Midazolam HCl in 5% Dextrose	Lack of sterility assurance.
87	Morphine Sulfate in 0.9% Sodium Chloride	Lack of sterility assurance.
88	Morphine Sulfate in 5% Dextrose	Lack of sterility assurance.
89	Lidocaine HCl	Lack of sterility assurance.
90	Fentanyl Citrate in 0.9% Sodium Chloride	Lack of sterility assurance.
91	SIH-Testosterone Cypionate 200 mg/mL Injectable	Lack of Assurance of Sterility: concerns of sterility assurance with the pharmacy's independent testing laboratory
92	Vancomycin PF (BSS) 1%	Lack of Assurance of Sterility: Pharmacy is recalling bevacizumab and vancomycin due to concerns of sterility assurance with the specialty pharmacy's independent testing laboratory.
93	Idoxuridine 0.1% Ophthalmic	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
94	Methotrexate Intraocular 400mcg 0.1cc	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
95	Methylcobalamin	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
96	Novarel (IM)	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
97	Papaverine 1nj 30mg/ml	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
98	Papaverine 12mg/phent 1mg/Pros 9mcq/ml	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
99	Prostaglandin all combinations	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.
100	Pyridoxine (p-f) 100mg/ml	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are not expired due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection.

Table 6. Enforcement reports due to LSA (n=1056).		
	Reason	**Numbers**
1	Lack of Sterility Assurance	184
2	Lack of Sterility Assurance: All lots of sterile products compounded by the pharmacy that are within expiry were recalled due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during a recent FDA inspection	121
3	Lack of Assurance of Sterility: The firm is conducting a voluntary recall of all compounded sterile preparations within expiry. The recall is being initiated in connection with a recent FDA inspection due to observations associated with certain quality control procedures that present a risk to sterility assurance	118
4	Lack of Assurance of Sterility: FDA inspectional findings resulted in concerns associated with quality control procedures that impacted sterility assurance	111
5	Lack of Assurance of Sterility: all sterile products compounded, repackaged, and distributed by this compounding pharmacy due to lack of sterility assurance and concerns associated with the quality control processes	103
6	Lack of Assurance of Sterility: The firm is recalling sterile compounded drugs within expiry due to lack of assurance of sterility	79
7	Lack of Assurance of Sterility: Sterility and stability data does not support expiry: recent inspection observations associated with certain quality control procedures that present a risk to sterility and quality assurance	65
8	Lack of Assurance of Sterility: The firm is recalling all sterile preparations within expiry due to deficient practices, which may have an impact on sterility assurance	59
9	Lack of Assurance of Sterility: Firm is recalling all unexpired lots of sterile compounded products after FDA inspection found concerns of lack of sterility assurance	43
10	Lack of Assurance of Sterility: A recall of all compounded sterile preparations within expiry is being initiated due to observations associated with poor sterile production practices resulting in a lack of sterility assurance for their finished drugs	39
11	Lack of Assurance of Sterility: Due to lack of documentation of proper environmental monitoring during the time in which the medication was produced, product produced on a day there was an excursion in environmental monitoring data, preliminary environmental monitoring report exceeds limits, therefore sterility cannot be assured, environmental monitoring report exceeds limits, therefore sterility cannot be assured.	32
12	Lack of Assurance of Sterility: Lack of sterility assurance in compounded aseptically filled injectable products	19
13	Lack of Assurance of Sterility: Possible yeast or mold contamination	11
14	Lack of Sterility Assurance: Microbial growth detected during a routine simulation of the manufacturing process. However, no batches of distributed product have been identified as actually containing microorganisms	10
15	Lack of Assurance of Sterility: concerns of sterility assurance with the pharmacy's independent testing laboratory	6
16	Lack of Assurance of Sterility: The firm expanded the recall to other injectable products due to lack of assurance of sterility from poor aseptic practices observed at the firm	6
17	Lack of Assurance of Sterility: Defective container resulting in the lack of sterility assurance	5
18	Lack of Assurance of Sterility: Three lots were released where there was a failure to follow proper testing and investigation procedures. Product may be out of specification (OOS) for endotoxin	5
19	Lack of Assurance of Sterility: The company has recalled Rohto Arctic, Rohto Ice, Rohto Hydra, Rohto Relief and Rohto Cool eye drops, due to concerns related to the quality assurance of sterility controls	5
20	Lack of Assurance of Sterility: The firms are recalling Lidocaine 1% PF Sterile Injection and EDTA disodium and Methylcobalamin 5 mg/mL, Multitrace-5 Concentrate, and Testosterone Cypionate (sesame oil) due to lack of assurance of sterility	5
21	Lack of Assurance of Sterility: The firm is voluntarily recalling certain pharmacy products due to lack of assurance of sterility concerns	5
22	Lack of Assurance of Sterility: leaking containers, which could lead to exposure to infectious agents	4
23	Lack of Assurance of Sterility: Company is recalling due bacterial contamination found after investigation at contract testing laboratory discovered that OOS/ failed results were reported to customers as passing. Hence, the sterility of these products cannot be assured	4
24	Lack of Assurance of Sterility: Product was found to be OOS for Antimicrobial Effectiveness testing (AET) at the 12 month-stability time point	3
25	Lack of Assurance of Sterility: The recall is being initiated due to a lack of sterility assurance and concerns associated with the quality control processes identified during an FDA inspection	3
26	Lack of Sterility Assurance: resulting from use of a damaged sterilizing filter for nitrogen used in the manufacturing process	2
27	Lack of Assurance of Sterility: During a routine simulation of the manufacturing of the product, a bacterial contamination was detected in some media fill units. No contaminated batches have actually been identified in the finished product, but there is a possibility of contamination	2
28	Lack of Assurance of Sterility: The firm is recalling all sterile preparations within expiry due to deficient practices, which may have an impact on sterility assurance	2
29	Lack of Sterility Assurance: A recent FDA inspection revealed poor aseptic production practices that result in lack of sterility assurance of products intended to be sterile	1
30	Lack of Sterility Assurance: A recent FDA inspection found that this product was not being compounded in an area appropriate for lyophilization, which may lead to a lack of sterility assurance	1
31	Lack of Assurance of Sterility: product not manufactured under sterile conditions as required for ophthalmic drug products	1
32	Lack of Assurance of Sterility: A particle excursion for a different batch of the same product may lead to a lack of sterility assurance	1
33	Lack of Sterility Assurance and Incorrect/Undeclared excipient: Product was found to contain undeclared colloidal silver	1

by compounded drugs with deficient cGMP procedures (121 recalls). Compounded drugs accounted for a large number of deviations. Out of 1056 citations, 523 (50%) were tracked to compounded products. Friedman[36] stated that three prevalent themes central to aseptic processing contamination are poor personnel practices, loss of environmental control, and flawed operational design. Looking at specific reasons in Table 6, most problems were related to faulty quality control procedures, unreliable sterility and stability data, lack of environmental monitoring, media fill failures, and possible yeast and mold contamination.

LSA was also the number one reason for sterile drug recalls in previous years.[10,11] Jimenez reported that 75% (71 out of 95) of sterile drugs were recalled by LSA.[10] Therefore, the numbers found in 2012-2019 were 10 times higher than previously reported. The fact that it was determined that the probability and risk of introducing microorganisms into products were beyond acceptable levels indicated the complete lack of process design and control.[36,37]

Sterilization is a process that removes and kills all microorganisms through a chemical agent or physical process.[30] However, there is no absolute certainty that all the units will be sterile. This is because not all units are tested for sterility. To provide that kind of degree of assurance, all units must be shown to be sterile. This cannot be accomplished unless all units are destroyed. Therefore, the sterility of a pharmaceutical lot is described as a probability where the likelihood of a contaminated unit or article is acceptably remote. Such a state of Sterility Assurance Levels (SAL) can only be established with adequate validated sterilization cycles and aseptic processing under appropriate cGMP. Furthermore, environmental monitoring of facilities, personnel, and processes is a major component during process control of sterile manufacturing and testing.

The likelihood of a product to be sterile is best explained in terms of the probability of microorganisms to survive the treatment process. For pharmaceutical sterilization procedures, the standard probability is less than one in one million units processed ($<10^{-6}$).[38] For instance, for a product containing 10^3 spores, an inactivation factor of 10^{-9} will be needed to give a sterility assurance level of 10^{-6}. This indicates that there is a probability of less than one in a million of microbial survivors to be present in a given sterile batch. Therefore, the sterilization process will need to produce a lethality level that will kill all microorganisms. Some of the most common procedures recommended to sterilize a product are:

- Filtration
- Steam sterilization
- Dry heat sterilization
- Ionizing irradiation
- Ethylene oxide

The choice depends on the capacity of the formulation and package to resist any of the above treatments. However, most of the drugs shown in Tables 5 and 6 were manufactured by aseptic processing.[5,30,37] Questionable package integrity increased the probability of microorganisms to compromise drug safety and potency (Table 6, reason 17). Deficient sterilization validation allowed the possibility of microbial survival and growth contaminating the finished drug product (Table 6, reason 10). Unsuccessful media fill operations resulting in contaminated vials indicated possible flaws in aseptic process design and execution (Table 6, reason 27). Improperly designed environmental monitoring program increased the risk of introducing microorganisms into the process resulting in major production losses (Table 6, reason 11). Unaudited contract-testing laboratory protocols and procedures endangered test reliability and compliance (Table 6, reasons 15 and 23). Non-validated processes to reduce and eliminate endotoxins from manufacturing resulted in OOS for endotoxins (Table 6, reason 18). Unreliable sterility and stability data compromised product's safety and efficacy (Table 6, reason 7). Improperly designed and non-validated processes increased the chance of microbial survival and contamination (Table 6, reasons 13, 23, 24). Deficient documentation and improper investigation procedures compromised data integrity and reliability (Table 6, reasons 11, 18). Improper facility and process design enhanced the risk of introducing microorganisms to processes and products (Table 6, reasons 30, 32). Poor aseptic practices during manufacturing compromised the sterility of products intended to be sterile (Table 6, reasons 16, 29).

Conclusions

Based upon publicly available FDA enforcement reports from June 2002-2019, microbial contamination control continues to be a major challenge for the pharmaceutical industry and regulatory agencies. Recalls due to *B. cepacia* and other bacterial species, mold, and LSA were higher than in previous years. Significant increases were also observed related to unidentified microbial contamination of non-sterile products. Enforcement activities appeared to be higher than in previous years specially when related to compounded drugs.

The FDA website provided a comprehensive search tool to analyze enforcement reports of non-sterile and sterile drugs. The remarkable improvements performed to the FDA website through the years facilitated and optimized data mining, navigation, and search of a large number of enforcement reports. These improvements provided the discovery of patterns and trends to organize information into a comprehensible structure for further analysis. The author is extremely grateful for the diligence of the FDA in providing a transparent and clear resource to ascertain the microbiological analysis of drug recalls.

The development and manufacturing of sustainable, safe, efficacious, and stable pharmaceutical products are major goals of the pharmaceutical industry. FDA enforcement data provided valuable information to determine the major sources of microbial contamination in drugs and current non-compliance practices in industry that led to major production losses, product recalls, and unfortunate incidents of morbidity and mortality. Learning from the information in the enforcement reports will provide effective and proactive approaches to eliminate improper practices leading to the optimization of process control and manufacturing of pharmaceutical products. The information also conveys the agency's current thinking on compliance and enforcement priorities.

by compounded drugs with deficient cGMP procedures (121 recalls). Compounded drugs accounted for a large number of deviations. Out of 1056 citations, 523 (50%) were tracked to compounded products. Friedman[36] stated that three prevalent themes central to aseptic processing contamination are poor personnel practices, loss of environmental control, and flawed operational design. Looking at specific reasons in Table 6, most problems were related to faulty quality control procedures, unreliable sterility and stability data, lack of environmental monitoring, media fill failures, and possible yeast and mold contamination.

LSA was also the number one reason for sterile drug recalls in previous years.[10,11] Jimenez reported that 75% (71 out of 95) of sterile drugs were recalled by LSA.[10] Therefore, the numbers found in 2012-2019 were 10 times higher than previously reported. The fact that it was determined that the probability and risk of introducing microorganisms into products were beyond acceptable levels indicated the complete lack of process design and control.[36,37]

Sterilization is a process that removes and kills all microorganisms through a chemical agent or physical process.[30] However, there is no absolute certainty that all the units will be sterile. This is because not all units are tested for sterility. To provide that kind of degree of assurance, all units must be shown to be sterile. This cannot be accomplished unless all units are destroyed. Therefore, the sterility of a pharmaceutical lot is described as a probability where the likelihood of a contaminated unit or article is acceptably remote. Such a state of Sterility Assurance Levels (SAL) can only be established with adequate validated sterilization cycles and aseptic processing under appropriate cGMP. Furthermore, environmental monitoring of facilities, personnel, and processes is a major component during process control of sterile manufacturing and testing.

The likelihood of a product to be sterile is best explained in terms of the probability of microorganisms to survive the treatment process. For pharmaceutical sterilization procedures, the standard probability is less than one in one million units processed ($<10^{-6}$).[38] For instance, for a product containing 10^3 spores, an inactivation factor of 10^{-9} will be needed to give a sterility assurance level of 10^{-6}. This indicates that there is a probability of less than one in a million of microbial survivors to be present in a given sterile batch. Therefore, the sterilization process will need to produce a lethality level that will kill all microorganisms. Some of the most common procedures recommended to sterilize a product are:

- Filtration
- Steam sterilization
- Dry heat sterilization
- Ionizing irradiation
- Ethylene oxide

The choice depends on the capacity of the formulation and package to resist any of the above treatments. However, most of the drugs shown in Tables 5 and 6 were manufactured by aseptic processing.[5,30,37] Questionable package integrity increased the probability of microorganisms to compromise drug safety and potency (Table 6, reason 17). Deficient sterilization validation allowed the possibility of microbial survival and growth contaminating the finished drug product (Table 6, reason 10). Unsuccessful media fill operations resulting in contaminated vials indicated possible flaws in aseptic process design and execution (Table 6, reason 27). Improperly designed environmental monitoring program increased the risk of introducing microorganisms into the process resulting in major production losses (Table 6, reason 11). Unaudited contract-testing laboratory protocols and procedures endangered test reliability and compliance (Table 6, reasons 15 and 23). Non-validated processes to reduce and eliminate endotoxins from manufacturing resulted in OOS for endotoxins (Table 6, reason 18). Unreliable sterility and stability data compromised product's safety and efficacy (Table 6, reason 7). Improperly designed and non-validated processes increased the chance of microbial survival and contamination (Table 6, reasons 13, 23, 24). Deficient documentation and improper investigation procedures compromised data integrity and reliability (Table 6, reasons 11, 18). Improper facility and process design enhanced the risk of introducing microorganisms to processes and products (Table 6, reasons 30, 32). Poor aseptic practices during manufacturing compromised the sterility of products intended to be sterile (Table 6, reasons 16, 29).

Conclusions

Based upon publicly available FDA enforcement reports from June 2002-2019, microbial contamination control continues to be a major challenge for the pharmaceutical industry and regulatory agencies. Recalls due to *B. cepacia* and other bacterial species, mold, and LSA were higher than in previous years. Significant increases were also observed related to unidentified microbial contamination of non-sterile products. Enforcement activities appeared to be higher than in previous years specially when related to compounded drugs.

The FDA website provided a comprehensive search tool to analyze enforcement reports of non-sterile and sterile drugs. The remarkable improvements performed to the FDA website through the years facilitated and optimized data mining, navigation, and search of a large number of enforcement reports. These improvements provided the discovery of patterns and trends to organize information into a comprehensible structure for further analysis. The author is extremely grateful for the diligence of the FDA in providing a transparent and clear resource to ascertain the microbiological analysis of drug recalls.

The development and manufacturing of sustainable, safe, efficacious, and stable pharmaceutical products are major goals of the pharmaceutical industry. FDA enforcement data provided valuable information to determine the major sources of microbial contamination in drugs and current non-compliance practices in industry that led to major production losses, product recalls, and unfortunate incidents of morbidity and mortality. Learning from the information in the enforcement reports will provide effective and proactive approaches to eliminate improper practices leading to the optimization of process control and manufacturing of pharmaceutical products. The information also conveys the agency's current thinking on compliance and enforcement priorities.

References

1. Jimenez, L. Microbial limits. In Microbial Contamination Control in the Pharmaceutical Industry. Luis Jimenez (Editor). Marcel Dekker Publishers, New York, N.Y., Chapter 2, 15-44, (2004).
2. Jimenez, L. Environmental monitoring. In Microbial Contamination Control in the Pharmaceutical Industry. Luis Jimenez (Editor). Marcel Dekker Publishers, New York, N.Y., Chapter 5, 103-132, (2004).
3. Federal Register of the United States of America. Code of Federal Regulations. Subpart F: Production and Process Control, 21 Part 211.113: Control of microbiological contamination, Rockville, Maryland, (2018).
4. Sandle, T. Microbial identification strategy for pharmaceutical microbiology. Journal of GXP Compliance 21, 11-20, (2017).
5. Singhal, T., Shah, S., Naik, R. Outbreak of *Burkholderia cepacia* complex bacteremia in a chemotherapy day care unit due to intrinsic contamination of an antiemetic drug. Indian Journal of Medical Microbiology 33, 117-119, (2015).
6. Centers for Disease Control and Prevention. Multistate outbreak of *Burkholderia cepacia* bloodstream infections associated with contaminated prefilled saline flush syringes. https://www.cdc.gov/hai/outbreaks/b-cepacia-saline-flush/index.html, (2016).
7. Marquez, L., Jones, K.N., Whatley, E.M., Koy, T.H., Revell, P.A., Taylor, R.S., Brooke Bernhardt, M., Wagner, J.L., Dunn, J.J., LiPuma, J.J., Cambell, J.R. An outbreak of *Burkholderia cepacia* complex infections associated with contaminated liquid docusate. Infection Control & Hospital Epidemiology 38, 567-573, (2017).
8. Becker, S.L., Berger, F.K., Feldner, S.K., Karilova, I., Haber, M., Mellmann, A., Schafers, H.J., Gartner, B. Outbreak of *Burkholderia cepacia* complex infections associated with contaminated octenidine mouthwash solution, Germany, August to September 2019. European Surveillance 23 (42):pii=1800540. https://doi.org/10.2807/1560-7917.ES.2018.23.42.1800540, (2018).
9. Underwood, E. Ecology of microorganisms as its affects the pharmaceutical industry. In W.B. Hugo and A.B. Russell eds. Pharmaceutical Microbiology, 6th Edition, Blackwell Science, Oxford, England, Chapter 17, 339-354, (1998).
10. Jimenez, L. Microbial diversity in pharmaceutical product recalls and environments. PDA Journal of Pharmaceutical Science and Technology 61, 383-399, (2007).
11. Sutton, S.W., and L. Jimenez. A review of reported recalls involving microbiological control 2004-2011 with emphasis on FDA considerations of "Objectionable Organisms". American Pharmaceutical Review 15, 42-57, (2012).
12. Ko, S., An, H.S, Bang, J.S., Park, S.W. An outbreak of *Burkholderia cepacia* complex pseudobacteremia associated with intrinsically contaminated commercial 0.5% chlorhexidine solution. American Journal of Infection Control 43, 266-268, (2015).
13. Cundell, A. Excluding *Burkholderia cepacia* complex from aqueous, non-sterile drug products. https://www.americanpharmaceuticalreview.com/Featured-Articles/358427-Excluding-i-Burkholderia-cepacia-i-complex-from-Aqueous-Non-Sterile-Drug-Products/, posted on February 12, (2019).
14. Rodley, P.D., Romling, U., Tummler, B. A physical genome map of the *Burkholderia cepacia* type strain. Molecular Microbiology 17, 57-67, (1995).
15. Juhas, M., Stark, M., Von Mering, C., Lumjiaktase, P., Crook, D.W., Valvano, M.A., Eberl, L. High confidence prediction of essential genes in *Burkholderia cenocepacia*. PLoS ONE 7(6): e40064. doi:10.1371/journal.pone.0040064, (2012).
16. Lessie, T.G., Hendrickson, W., Manning, B.D., Devereaux, R. Genomic complexity and plasticity of *Burkholderia cepacia*. FEMS Microbiology Letters 144, 117-128, (1996).
17. Rushton, L., Sass, A., Baldwin, A., Dowson, C.G., Donoghue, D., Mahenthiralingam, E. Key role for efflux in the preservative susceptibility and adaptive resistance of *Burkholderia cepacia* complex bacteria. Antimicrobial Agents and Chemotherapy 57, 2972-2980, (2013).
18. Devanga, N.K., Veeraraghavan, B. Accurate identification and epidemiological characterization of Burkholderia cepacia complex: an update. Ann. Clin. Microbiol. Antimicrob. Feb 4. doi: 10.1186/s12941-019-0306-0, (2019).
19. Jimenez, L., Jashari, T., Vasquez, J., Zapata, S., Bochis, J., Kulko, M., Ellman, V., Gardner, M., Choe, T. Real-Time PCR detection of Burkholderia cepacia in pharmaceutical products contaminated with low levels of bacterial contamination. PDA Journal of Pharmaceutical Science and Technology 72:73-80, (2018).
20. Jimenez, L., Smalls, S. Molecular detection of *Burkholderia cepacia* in toiletry, cosmetic and pharmaceutical raw materials and finished products. Journal of AOAC International 83, 963-966, (2000).
21. Attia, M.A., Ali, A.E., Essam, T.M., Amin, M.A. Direct detection of *Burkholderia cepacia* in susceptible pharmaceutical products using semi-nested PCR. PDA Journal of Pharmaceutical Science and Technology 70, 99-108, (2016).
22. Torbeck, L., Raccasi, D., Guilfoyle, D. E., Friedman, R. L., Hussong, D. *Burkholderia cepacia*: This decision is overdue. PDA Journal of Pharmaceutical Science and Technology 65, 535–543, (2011).
23. Cundell, A.M. Mold monitoring and control in pharmaceutical manufacturing areas. https://www.americanpharmaceuticalreview.com/Featured-Articles/190686-Mold-Monitoring-and-Control-in-Pharmaceutical-Manufacturing-Areas/, posted July 30, (2016).
24. Jimenez, L., Smalls S., Ignar R. Use of PCR analysis for detecting low levels of bacteria and mold contamination in pharmaceutical samples. Journal of Microbiological Methods. 41, 259-65, (2000).
25. Ahearn, D.G., Stulting, R.D. Moulds associated with contaminated ocular and injectable drugs: FDA recalls, epidemiology considerations, drug shortages, and aseptic processing. Medical Mycology 56, 389-394, (2018).
26. Smith, R.M., Schaefer, M.K., Kainer, M.A., Wise, M., Finks, J., Duwve, J., Fontaine, E., Chu, A., Carothers, B., Reily, A., Fiedler, J., Wiese, A.D., et al. Fungal infections associated with contaminated methylprednisolone injections. New England Journal of Medicine 369, 1598-1609, DOI: 10.1056/NEJMoa1213978, (2013).
27. Sandle, T. Fungal contamination of pharmaceutical products: the growing menace. European Pharmaceutical Review 19, 68-71, (2014).Cundell, A.M. Microbial identification strategies in the pharmaceutical industry. PDA Journal of Pharmaceutical Science and Technology 60, 111-23, (2006).
28. Jimenez, L. Molecular applications to pharmaceutical processes and clean room environments. PDA Journal of Pharmaceutical Science and Technology 65, 242-253, (2011).
29. Jimenez, L. Sterility testing and sterility procedures. In Microbial Contamination Control in the Pharmaceutical Industry. Luis Jimenez (Editor). Marcel Dekker Publishers, New York, N.Y., Chapter 4, pages 77-102, (2004).
30. Jimenez, L., Ignar, R., D'Aiello, R., Grech, P. Use of PCR analysis for sterility testing in pharmaceutical environments. Journal of Rapid Methods and Automation in Microbiology 8, 11-20, (2000).
31. Gray, J.C., Morandell, D., Gapp, G., Le Goff, N., Neuhaus, G., Staerk, A. Identification of microorganisms after Milliflex rapid detection-A possibility to identify nonsterile findings in the Milliflex rapid sterility test. PDA Journal of Pharmaceutical Science and Technology 65, 42-54, (2011).
32. Smith, R., Von Tress, M., Tubb, C., Vanhaecke, E. Evaluation of the ScanRDI as a rapid alternative to the pharmacopoeial sterility test method: comparison of the limits of detection. PDA J. Pharm. Sci. Technol. 64, 356-363, (2010).
33. Jimenez, L., Rana, N., Amaraj, J., Walker, K., Travers, K. Validation of the BacT/ALERT® 3D system for rapid sterility testing of biopharmaceutical samples. PDA J. Pharm. Sci. and Technol. 66, 38-54, (2012).
34. U.S. Food and Drug Administration. Guidance on sterile drug products produced by aseptic processing. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice, September, (2004).
35. Lolas, A.G., Metcalfe, J. Evaluation of microbial growth potential of pharmaceutical drug products and quality by design. PDA Journal of Pharmaceutical Science and Technology 65, 63-70, (2011).
36. Friedman, R.L. Aseptic processing contamination case studies and the pharmaceutical quality system. PDA Journal of Pharmaceutical Science and Technology 59, 118-126, (2005).
37. Woedtke, T., Kramer, A. The limits of sterility assurance. GMS Krankenhhyg Interdiszip. 3(3): Doc19. Published online 2008 Sep 3. PMCID: PMC2831250, (2008)