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Microbial Control of Pharmaceutical Raw Materials

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Abstract

Microbial contamination control of pharmaceutical products is a great challenge. In this article, different sources of microbial contamination have been identified including microbial contamination of pharmaceutical products due to contamination from raw materials. This microbial contamination can significantly impact patient's health and thus trigger recall of products. In this article, prevention of microbial contamination from raw materials are mentioned which could ensure safety of patient's health as well as prevent recall of products.

Keywords: Microbial contamination, raw materials, pharmaceuticals

Introduction

Sometimes people say, microbial contamination is never ending issue and they feel frustrated. From 2018 until the present, there have been a total of 37 recalls due to microbial contamination, as verified by the FDA[1]. Between 2012 and 2019, 87% of recalls for sterile pharmaceuticals were related to unknown microbial contamination[2].

Between 2014 and 2017, the FDA received 197 reports of adverse events related to intrinsic microbiological or fungal contamination, and 32 of those reports documented serious adverse patient outcomes, according to their Guidance for Industry: Microbiological Quality Considerations in Non-Sterile Drug Manufacturing.

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The actual number of drug items that are produced and then rejected due to microbial contamination before they might be delivered is much higher than the number of lots where microbial contamination is found. Results from microbial enumeration tests on other lots of drug products have shown CFU numbers below the drug's standard, allowing for release. These bacteria may be able to change to the new drug form during storage, making it more potent than the original. Because of the uneven distribution of potential microbial contamination, a drug sample could have no microorganisms present yet still be contaminated, and drug products that satisfied microbiological test standards could be released despite having an unfavorable effect on patients' health. This is true both for sterile and nonsterile pharmaceuticals.

The deterioration and reduced efficacy of a drug can be caused by microorganism contamination. Patients, especially those with impaired immune systems, are at risk of being exposed to pathogens or opportunistic microorganisms that can result in severe metabolic harm or even death. Microbial toxins are produced by some microorganisms, and they can be extremely dangerous to the patient.

What causes Microbial Contamination

Most cases of microbial contamination in recalled pharmaceuticals are caused by Burkholderia. Currently, there are more than 80 species of Burkholderia that have been scientifically described. *Burkholderia pseudomallei, Burkholderia mallei, Burkholderia cepacia* complex, and *Burkholderia gladioli* are the only species of Burkholderia considered to be human pathogens. These microorganisms are Gram-negative bacilli that are aerobic, nonspore-forming, and nonfermenting. Only *B. mallei*, a pathogen that can live inside of hosts, is not naturally occurring in the environment. Because *B. pseudomallei* may infect both humans and animals, it is considered a "tier 1 select agent" by the U.S. Centers for Disease Control and Prevention (CDC).

Poisoning incidents caused by bongkrekic acid (BA), one of the metabolites of the *Burkholderia gladioli* pathovar cocovenenans (*B. cocovenenans*), have been reported in Indonesia, Mozambique and China. It is an odorless, tasteless heat-stable

polyketide. A lethal dose of BA — between 1 mg/kg and 3.16 mg/kg — can kill within 1–10 hours after exposure.

Bacillus cereus is associated mainly with food poisoning and serious eye infections but can cause a serious and sometimes fatal infection that produces tissue destructive exoenzymes and toxins. It is a deadly nosocomial infection that is taken seriously in hospitals[3].

Pseudomonas fluorescens can cause bacteremia infections and has been associated with Crohn's disease[4].

Ralstonia pickettii is a persistent Gram-negative nosocomial infectious organism that takes advantage of underlying patient conditions and diseases[5].

Gluconacetobacter liquefaciens is a Gram-negative plant pathogen that has only been associated with infection of immunocompromised patients[6].

We may assume that Burkholderia wouldn't make it through processing or that BA contamination wouldn't be an issue, but many of the raw materials required to make medications are produced in Asia and India. The raw materials we utilize to produce pharmaceuticals may include Burkholderia or other strong poisons.

There is more to the story than the fact that many instances of microbial contamination can be traced back to in-process contamination during drug product manufacture. After a column-purification step, *Klebsiella oxytoca*, a bacteria typically found in biofilms, was detected in a process stream. This organism was reported to produce a cytotoxin in isolated samples; hence, a batch of API was deemed unusable. Another case involved *B. cepacia* contamination of docusate sodium oral solution lots traced back to a water supply used in production.

The main sources of microbial contamination of drug products are:

- Raw materials and components
- Lack of effective cleaning and in-process controls
- Humans

- Container closure system failures
- Sterilization failures

Raw Material and Component Contamination

In this article, our discussion is limited to microbial contamination control of raw materials and components.

Some manufacturers think that chemical processing eliminates the need for microbiological controls on active pharmaceutical ingredients (APIs) and excipients (Excipients) used in the production of pharmaceuticals. The same justification is made for components, cleaning materials, and other ancillary drug manufacturing supplies. Actually, this is not true, chemical processing is not sufficient to eliminate microbiological contamination.

There are a number of APIs and excipients that support microbial growth under the correct conditions. Testing reveals that naturally derived substances, such as plant extracts, include high quantities of bacteria, molds, and yeast. Uncontrolled fermentation products may potentially contain microbial toxins and metabolic contaminants.

APIs and excipients are distributed over lengthy supply chains wherein contamination may be introduced through the use of incorrectly cleaned containers, substandard containers that do not adequately protect the ingredients, or during transport and storage. Moisture from rain at an airport ramp or leaking warehouse roofs, vermin infestation, and damaged containers are further transportation-related risks.

Since they are not producing a sterile product, many API and excipient manufacturers do not believe that sanitation and environmental controls are necessary. But actually, sanitation and environmental controls are also necessary for non-sterile facilities.

Another cause of microbial contamination is water. Water is employed in numerous raw-material and drug-product production processes and is a substantial element in many injectable and oral drugs on its own.

There is a need for effective microbiological contamination control measures because there are so many sources of raw materials and ingredients originating from various countries, companies, and manufacturing processes. This pertains to the raw materials, ingredients, and manufacturing aids utilized in the production of pharmaceuticals.

The following contamination control strategies have been proven effective and are recommended for implementation by the manufacturers of the raw materials[7]:

- Design of manufacturing processes that minimize microbial contamination
- Microbial risk assessment of raw materials and ingredients
- Development of effective audit checklists for suppliers focused on microbial control
- In-person audits of manufacturers
- Supplier quality agreements established with a focus on microbial control
- Control of storage conditions in warehouses and during transit
- Control of processing times
- Effective maintenance of facilities and equipment
- Effective cleaning of equipment and facilities
- Minimization of contact with humans
- Control of vermin and insects
- Control of containers used to store and ship materials
- Control of supply chain
- Control of water systems
- Control of wastewater and waste
- Development of pasteurization or sterilization processes for natural ingredients
- Development of microbial test methods and specifications based on risk assessments
- Effective investigation of microbial contamination of drug products

Conclusion

Significant microbiological contaminations of drug products continue to be an industry concern, as seen by the recall and enforcement data. Existing microbiological contamination control methods must be implemented to the raw materials and APIs utilized in the production of pharmaceuticals.

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