THE IMPORTANCE OF ACCURATE AND RELIABLE IDENTIFICATIONS

EVERY STEP OF THE WAY

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FEDERALLY MANDATED REGULATIONS
PRODUCT AND PROCESS CONTROL – MANAGING RISKS

Establish a Quality system for the manufacturing process **control points** and thus ensure the purity of the product

Establish a testing program that monitors levels of microorganisms at key places in the facility for purposes of monitoring the state of **environmental control**

ELEMENTS OF RISK BASED APPROACH

Are of microorganisms present in the product? Sterility; alert/action levels

What organisms are present in manufacturing environment and where?

Identity of microorganisms- Objectionable?

Are organisms transient or resident?

Accuracy of ID methods affects the efficacy of your approach.

IS THE SAMPLE ROUTINE OR CRITICAL?

Bioburden

Sterility

Water

Environmental monitoring

Method validation

Preservative efficacy

ENVIRONMENTAL MONITORING

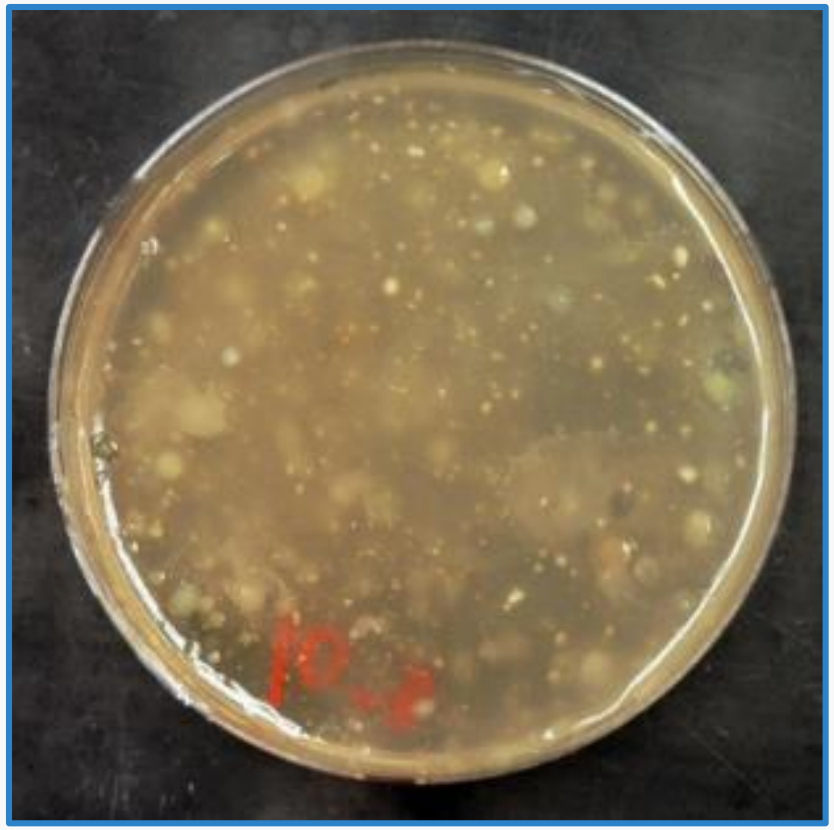
Verify that process are controlled

Baseline profile of a manufacturing environment

Early warning to detect possible trends

Identifies sites at risk

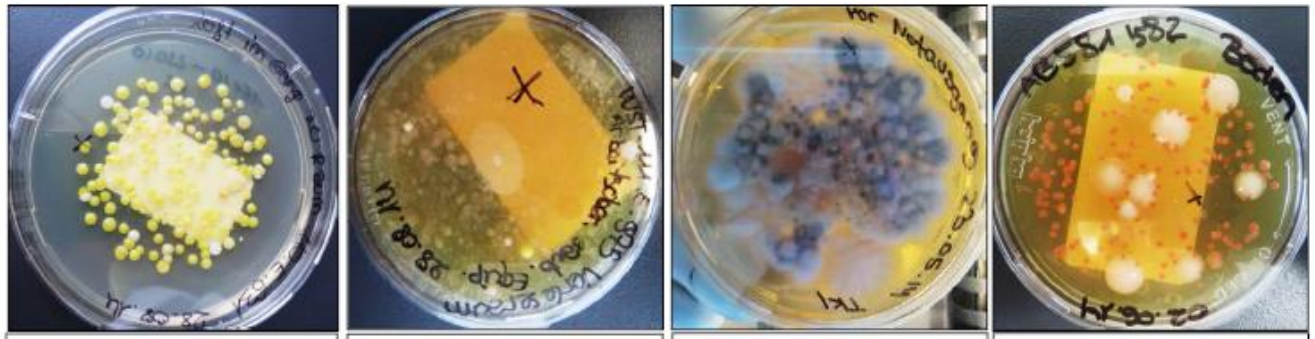
Document state of control



ROUTE CAUSE ANALYSIS AND CAPA

Standard actions – Identification Microorganisms

Root cause investigation



Human	Spores (bacilli)	Mould	Water
- Too many persons? - Technician? Visitors? - Strong germ carrier? - Behavior correctly? - Gowning correctly? - Re-contamination after disinfection? - HVAC sufficient?	- Material contaminated? - Cardbord boxes, wooden pallets? - Leakages? - Disinfectant contaminated?	- Surface disinfection correct? - Material contaminated? - Cardbord boxes, wooden pallet? - Leakages?	- Cleaning / disinfection correctly? - Re-contamination? - Leakage?

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ROBUSTNESS OF A QUALITY SYSTEM

What is the product?

- Sterile
- Non-sterile
- Mode of delivery, inhibitory properties, intended patients

What ID confidence is needed for different areas and sources?

- Loading dock
- Reagent prep
- Media fill room
- Final product

Prioritize and correlate the criticality of the samples with the ID method

WHAT IS AN OBJECTIONABLE MICROORGANISM?

THE QUESTION OF "OBJECTIONABLES" IN NON-STERILE PRODUCTS

FDA requires regulated non-sterile products to be free of objectionable organisms

This can be defined several ways:

- Pathogenicity
  - Primary
  - Compromised population
  - Toxins
- Indicative of process problems
- Compromise product efficacy

Microbial Limits Tests do not meet this FDA requirement

Identification yields essential information

TECHNOLOGY/APPLICATION

Microbial Diversity in Pharmaceutical Product Recalls and Environments

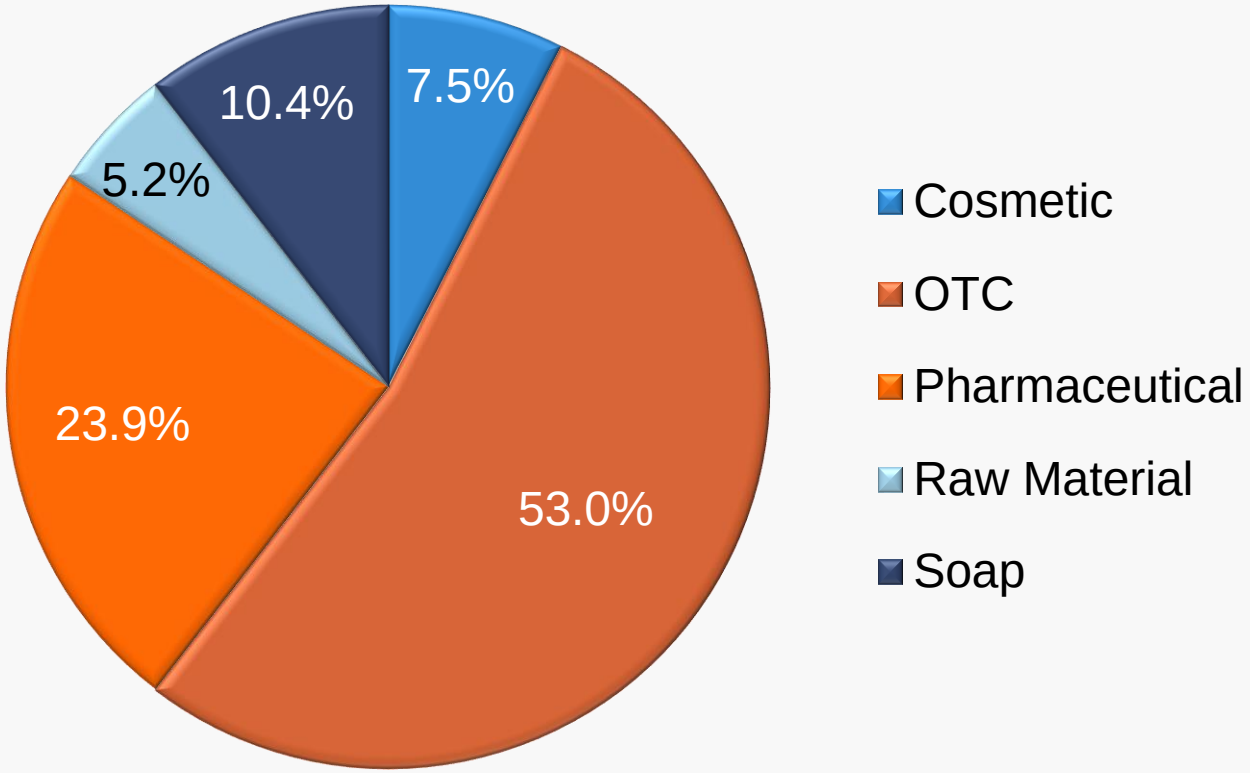
LUIS JIMENEZ

ABSTRACT: Identification of microbial contaminants in product recalls and environmental samples provides important information on the possible contamination sources and distribution of microbial species in pharmaceutical environments. Analysis of FDA product recall data for 134 non-sterile pharmaceutical products from 1998 to September 2006 demonstrated that 48% of recalls were due to contamination by either *Burkholderia cepacia*, *Pseudomonas* spp., or *Ralstonia picketti*, while yeast and mold contamination were found in 23% of recalls. Gram-negative bacteria accounted for 60% of recalls, but only 4% were associated with Gram-positive bacteria. Of the 193 recalls of sterile products, 78% were due to the lack of sterility assurance and 7% for yeast and mold contamination. For sterile products, Gram-negative bacteria accounted for 6% of recalls, with only 1% due to Gram-positive bacteria. For non-sterile and sterile products, *B. cepacia* was the most frequently isolated microbial species with 22% and 2.5% of recalls, respectively. Based upon the review of the scientific literature, *B. cepacia*, *Pseudomonas* spp., or *Ralstonia picketti* may be associated with water contamination, while yeast and mold and Gram-positive bacteria may have indicated deficient environmental controls. The presence of unculturable microbial populations in pharmaceutical waters and clean rooms was reported, but no evidence has been published that product quality was negatively affected.

PDA J Pharm Sci Technol. 2007 Sep-Oct;61(5):383-99.

JIMENEZ RECALL REVIEW – 1998-2006

Product Categories Involved in Recalls



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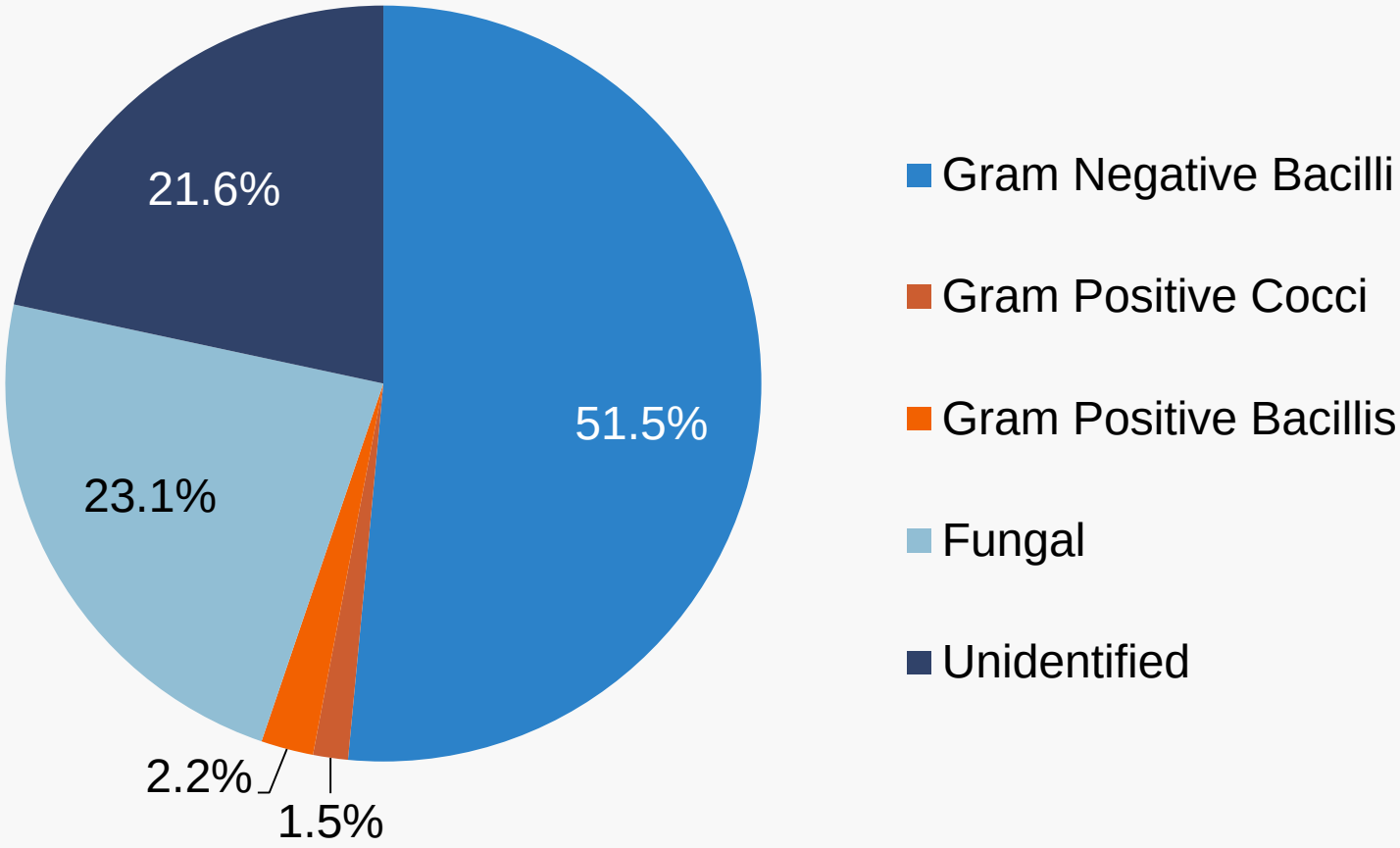
JIMENEZ RECALL REVIEW – 1998-2006

Microorganisms Involved in Recalls



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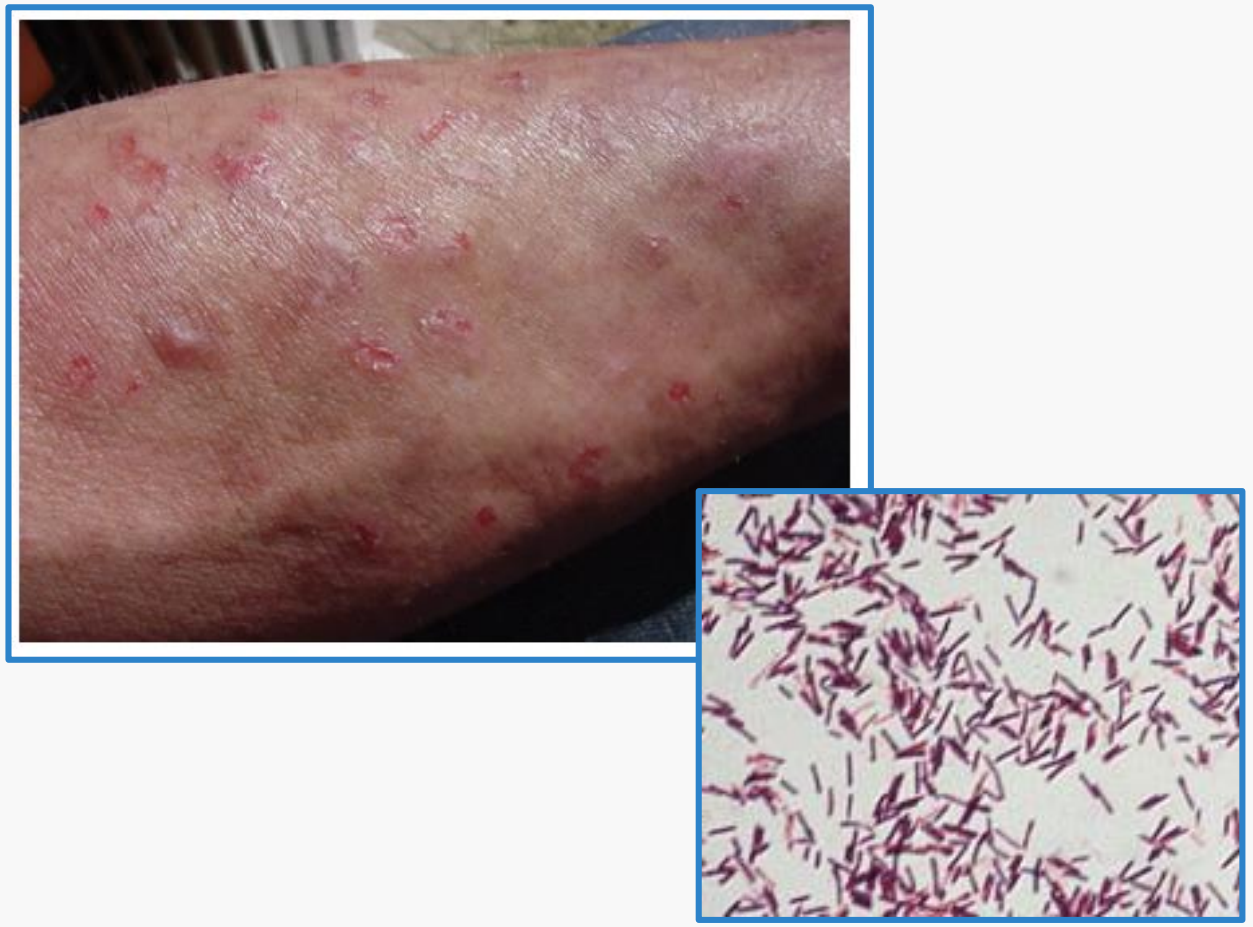
BACILLUS CEREUS

Bacillus cereus is a Gram-positive spore-forming bacterium responsible for two types of food-assoc. intoxications from enterotoxin: an emetic and a diarrheal syndrome. Rare but severe opportunistic infections have been attributed to *B. cereus*



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HOW TO DETERMINE IF A MICROORGANISM IS OBJECTIONABLE?

Must have a plan for identifying all microorganisms in addition to the specified objectionable organisms.

Organisms listed in the USP ***does not*** satisfy the definition of objectionable microorganisms.

Objectionable organisms are specific to the product and application

There is ***no*** published list and the list would be ever evolving as new pathogens emerge that are associated with disease or affect efficacy

RELATIVE MERITS OF IDENTIFICATION SYSTEMS

Throughput

Cost of consumables

Labor requirements

Size of microorganism identification database

Facility requirements

Compatibility with existing systems

Need for physiological information

Purpose

- Routine ID
- Investigations