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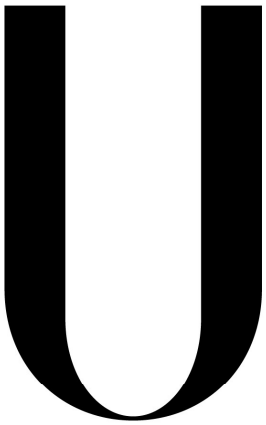

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# EVALUATION OF THE MICROBIOLOGICAL CONTAMINATION OCCURRENCE IN THE PHARMACEUTICAL INDUSTRY

Dissertation to obtain the Master Degree of Science in Pharmaceutical Engineering

Lisbon 2016

Ana Marta Corrêa dos Santos

Supervisors: Mestre Mara Saavedra and Professor Dr. António J. Almeida (FFUL)

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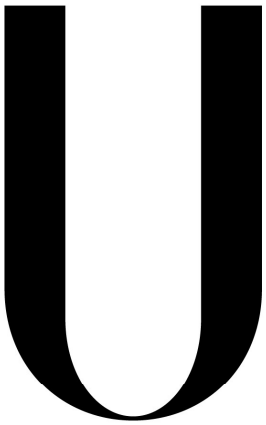

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## Abstract

EVALUATION OF THE MICROBIOLOGICAL CONTAMINATION OCCURRENCE IN THE PHARMACEUTICAL INDUSTRY

Microbial contamination of non-sterile drug products began to be a concern in the 1960's when diseases outbreaks were associated with bacterial and fungal contamination of drug preparations. Currently, microbiological contamination is still a frequent problem and is part of top ten causes responsible for recalls in USA and UK market. To better understand this issue and define what can be done is necessary to know the microbial hazards involved in the manufacturing process and identify the root causes. Here we present a Quality Risk Management approach to describe this relevant problem. To identify the hazards, a survey was conducted using reports of drug products recalls and warning letters registered between 2008 to February 2016. Recalls data were collected from FDA and MHRA databases to find occurrences involving microbial contamination of non-sterile drug products. Failure Modes obtained were analyzed through Pareto chart. Warning letters were collected from FDA and EMA databases to identify violations in Good Manufacturing Practice that represents a microbial hazard. The results were evaluated using a 6M Ishikawa diagram, a Preliminary Hazard Analysis (PHA), and a Failure Mode Effects, Critically Analysis (FMECA). PHA and FMECA were conducted with the cooperation of a sample of 14 representative Portuguese pharma companies (ISO committee). The severity, likelihood of occurrence and difficulty of detection of the harms were classified into three categories: low, moderate and high. Risks were defined as the combination of these three parameters. Results obtained shows that manufacturers of non-sterile drug products should be alert for some potential root causes such as raw material, preservatives, and water. With the risk assessment conducted in this study, it was possible to develop a microbial Risk Ranking Index and a Risk Priority Rank based on the real situation found in many companies. These results allow a manufacturer to develop further this analysis and define how these issues can best be prevented and which mitigations actions need to be implemented.

**Keywords**: Quality Risk Management, Microbiological Contamination, Recalls, Warning Letters, Non-Sterile Drug Products.

## Resumo

AVALIAÇÃO DA OCORRÊNCIA DA CONTAMINAÇÃO MICROBIOLOGICA NA INDÚSTRIA FARMACÊUTICA

A contaminação microbiológica de produtos não estéreis passou a ser preocupação das indústrias e agências regulatórias na década de 60, quando surtos de doenças foram associados a contaminação bacteriana e fúngica de medicamentos. Atualmente, a contaminação microbiológica é uma das dez causas responsáveis por recolhas de medicamentos não estéreis nos Estados Unidos e no Reino Unido. Para melhor entender essa questão e definir o que pode ser feito para amenizar e reduzir esse problema é necessário conhecer os riscos microbiológicos envolvidos no processo e as causas raízes das recolhas. Este trabalho apresenta uma abordagem baseada em análise de risco para descrever e evidenciar os riscos microbiológicos mais relevantes. Para identificar os riscos existentes, foi realizada uma pesquisa em recolha de medicamentos não estéreis e cartas de advertências registradas entre 2008 a fevereiro de 2016. As recolhas analisadas são provenientes de bases de dados do FDA e MHRA, os dados obtidos foram analisados por meio de diagrama de Pareto. As cartas de advertências são provenientes das bases de dados do FDA e EMA e foram tratadas através do Diagrama de Ishikawa usando categorias 6M e ferramentas de gestão de risco, como *Preliminary Hazard Analysis* (PHA) e *Failure Mode Effects, Critically Analysis* (FMECA). A avaliação do risco foi realizada com as ajuda do grupo ISO, um grupo formado por 14 representantes de indústrias farmacêuticas de Portugal. A severidade, probabilidade de ocorrência e dificuldade de detecção das não-conformidades identificadas foram classificadas em três categorias: baixo, mediano e alto. O risco foi definido como a combinação dos três parâmetros. Os resultados obtidos mostram que os fabricantes de medicamentos não estéreis devem ter em consideração as seguintes potenciais fontes de contaminação, matéria prima, os conservantes e a água. Com a avaliação de riscos realizada neste estudo, foi possível desenvolver uma lista de riscos e prioridades com base na situação real encontrada em muitas empresas. Essa classificação permite que as indústrias possam desenvolver uma análise mais detalhada e propor ações de redução e mitigação da contaminação microbiológica proporcionais com os riscos aqui ressaltados.

**Palavra Chave:** Gestão de Risco, Contaminação Microbiológica, recolhas, Cartas de advertência, Medicamentos não estéreis.

# AVALIAÇÃO DA OCORRÊNCIA DA CONTAMINAÇÃO MICROBIOLOGICA NA INDÚSTRIA FARMACÊUTICA

## Introdução

A contaminação microbiológica de medicamentos representa um grande risco para a saúde de pacientes. Na literatura é possível encontrar muitos exemplos de surtos de doenças ligadas a medicamentos contaminados por bactérias e fungos. Atualmente, apesar de existir uma legislação mais rigorosa, a contaminação microbiológica ainda é motivo de preocupação visto que é uma das dez causas responsáveis por recolhas de medicamentos não estéreis nos Estados Unidos e no Reino Unido. Além de causar danos aos pacientes e prejudicar a adesão ao tratamento, a presença de microrganismos em medicamentos pode denegrir a imagem da empresa e causar grandes prejuízos financeiros. Desta forma, para lidar com o problema desta dimensão, este trabalho propõe uma abordagem baseada no risco, ou seja, a identificação, análise e avaliação de riscos por meio de ferramentas de gestão de risco como PHA e FMECA.

## Objetivo

O presente trabalho possuí três principais objetivos, (1) investigar a ocorrência e as causas raízes das recolhas relacionadas com a contaminação microbiológica, (2) avaliar os perigos de contaminação microbiológicas envolvidos no processo de fabrico de medicamentos não estéreis (3) usar ferramentas de gestão de risco para destacar e analisar os riscos considerados altos e ainda fornecer informações de base científica para apoiar a tomada de decisão e permitir a priorização de ações de mitigação.

## Metodologia de pesquisa

Para a análise das recolhas relacionadas com contaminação microbiológica foi realizado uma pesquisa nas bases de dados do FDA e MHRA, refletindo assim a realidade dos mercados farmacêuticos dos Estados Unidos e Reino Unido. Para a análise dos perigos microbiológicos existentes no processo de fabrico buscou-se cartas de advertências emitidas pelo FDA e EMA após inspeções sanitárias. Somente foram analisadas cartas destinadas a indústrias produtoras de medicamentos não estéreis. O período avaliado foi entre 2008 a fevereiro de 2016.

A análise dos dados ocorreu por meio de ferramentas de Gestão de Risco como PHA, FMECA, diagrama de Ishikawa e diagrama de Pareto. As recolhas foram analisadas através do diagrama de Pareto, que foi utilizado com o intuito de estudar as principais causas responsáveis e suas respectivas contribuições para a recolha dos medicamentos. As cartas de advertências foram analisadas através do diagrama de

Ishikawa, PHA e FMECA. O diagrama de Ishikawa permitiu organizar as não conformidades encontradas nas cartas de advertência em grupos e assim estudar as causas e os efeitos.

PHA e FMECA foram usadas para analisar os perigos microbiológicos envolvidos no processo de fabrico e construir uma classificação de riscos e prioridade. A severidade, ocorrência e dificuldade de detecção das não conformidades foram definidas com a ajuda de um grupo formado por 14 representantes de indústrias farmacêuticas em Portugal (grupo ISO). O grupo classificou cada não conformidade de acordo com três níveis, baixo, mediano e alto. O risco foi definido como a combinação dos três fatores.

**Resultados - FDA**

Os resultados obtidos para as recolhas mostram que a contaminação microbiológica é motivo de preocupação. Nos Estados Unidos essa causa foi responsável por aproximadamente 6% das recolhas de medicamentos não estéreis e constituiu uma das 10 principais razões.

O mercado americano registrou 101 recolhas de medicamentos não estéreis devido a contaminação microbiológica entre os anos de 2008 a fevereiro de 2016. Os microrganismos mais citados foram a *Burkholderia cepacia* e fungos (Mofo e bolores). Dentre as causas justificadas para a recolha dos medicamentos, a contaminação da matéria prima e a falha dos conservantes foram as mais expressivas, e foram responsáveis por respectivamente 19% e 8% das recolhas.

Os resultados obtidos com as cartas de advertências emitidas pelo FDA mostram que as falhas mais cometidas pelas indústrias estão relacionadas com (1) falta de procedimentos de controle que garantam os parâmetros de qualidade do medicamento produzido, 18 cartas; (2) falha em justificar e investigar qualquer discrepância ocorrida no processo de fabrico, 15 cartas; (3) Inadequação dos testes de estabilidades, 13 cartas.

A análise realizada através do diagrama de Ishikawa mostrou que a maior parte das não conformidades são decorrentes dos Métodos (33%) e da mão de obra (27%). Estes resultados mostram que grande parte das causas estão relacionadas com a forma como o processo é realizado e com os requisitos específicos para fazê-lo, tais como políticas, procedimentos, metodologias, normas, regulamentos e leis. A falha com a mão de obra sinaliza que os colaboradores não seguem os procedimentos e, portanto, não estão aptos a executarem tais tarefas.

Resultados obtidos com o PHA mostram que as não conformidades que receberam maior pontuação de risco são (1) falha em demonstrar a confiabilidade da

análise do fornecedor por meio da validação adequada dos resultados dos testes em intervalos apropriados, 9 pontos; (2) falha em estabelecer tempo para as atividades e ainda em garantir a qualidade do produto final, 9 pontos; (3) falha em estabelecer e seguir os procedimentos de controle adequados para monitorar a saída e para validar o desempenho dos processos de fabricação, 9 pontos.

O ranking de prioridades construído através da FMECA, mostrou que apenas uma não conformidade recebeu a maior pontuação (27 pontos) foi a "falha em estabelecer e seguir os procedimentos de controle adequados para monitorar a saída e para validar o desempenho dos processos de fabricação".

**Resultados – EMA e MHRA**

O mercado britânico apesar de possuir um menor espaço amostral, teve resultados similares ao mercado americano. No Reino Unido, 94 recolhas foram registradas entre 2008 e fevereiro de 2016. Deste total, 50% foram de medicamentos não estéreis. A contaminação microbiológica de medicamento não estéreis foi responsável por três recolhas. As recolhas registradas pelo MHRA também citam Fungos como microrganismos responsáveis, contaminação da matéria prima e a falha do conservante como possíveis razões.

Os resultados obtidos com as cartas de advertência emitidas pela EMA mostram que não conformidades mais cometidas foram (1) falha em garantir a integridade e veracidade dos dados recolhidos, 11 cartas; (2) falhas no cumprimento das BPF, 10 cartas; (3) falha em investigar os desvios, 8 cartas.

O diagrama de Ishikawa realizado mostra que as falhas identificadas pela EMA estão mais distribuídas entre as categorias 6M que as falhas identificadas pelo FDA. Entretanto, as categorias que agruparam o maior número de não conformidades são as mesmas que o FDA, ou seja, a mão de obra (27%) e os métodos (25%). As falhas relacionadas com a mão de obra, mostram que os colaboradores não seguem os procedimentos existentes e, portanto, não estão aptos a executarem tarefas específicas. As falhas relacionadas com os métodos mostram que existem problemas no processo produtivo dos medicamentos ou nos requisitos necessários para a produção.

Resultados obtidos com o PHA mostram que as não conformidades que receberam maior pontuação de risco são (1) falha em investigar resultados fora da especificação, 15 pontos; (2) procedimentos de validação de limpeza inapropriados, 15 pontos; (3) deficiência na gestão das reclamações, 15 pontos; (4) falhas na atualização dos acordos de qualidade, 15 pontos.

A classificação de prioridades construída com a FMECA apontou três não conformidades como sendo de 1ª prioridade (1) falhas na atualização dos acordos de

qualidade, 45 pontos; (2) falha nos treinamentos dos colaboradores, 27 pontos; (3) falha em investigar os desvios, 27 pontos.

**Conclusão**

A conclusão que se obtém com esse estudo é que para medicamentos não estéreis os perigos mais evidentes estão relacionados com a falha dos conservantes e com a qualidade das matérias primas usadas, em especial a água que é um importante reservatório de bactérias do gênero *Burkholderia*, microrganismo frequentemente citado nas recolhas nos Estados Unidos.

Muitas das falhas cometidas pelas indústrias farmacêuticas e registradas nas cartas de advertência têm impacto direto e indireto na contaminação microbiológica de medicamentos e, portanto, devem ser avaliadas com atenção.

A classificação e priorização dos riscos desenvolvida com as ferramentas PHA e FMECA, mostraram que as falhas que receberam maiores pontuações na escala usada constituem real perigo para a contaminação microbiológica de medicamentos, visto que estão conectadas direta ou indiretamente com as causas de recalls analisados.

Com a avaliação do risco realizada neste estudo, foi possível desenvolver uma classificação de risco microbiológico com base na situação real encontrada em muitas empresas. Essa classificação permite que um fabricante possa desenvolver análises mais detalhadas e definir formas para evitar e mitigar a contaminação microbiológica em suas fabricas.

Dedico este trabalho ao Dr. Manoel.
Além de grande pai, é meu melhor e maior Professor.

## Agradecimentos

Gostaria de agradecer a minha família, que mesmo de longe me apoiou e ajudou com essa conquista. Pai e mãe pelo apoio incondicional nas minhas decisões. Mariabel, Pedro e Jaouhar pelas horas de descontração e palavras de incentivo. As famílias Teixeira e Tigeleiro que foram um porto seguro e de aconchego em Portugal. Aos colegas de mestrado que sempre ajudaram na adaptação.

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Obrigada por tornarem possível este trabalho.

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## Abbreviations

| | |
|---|---|
| AET | Antimicrobial Effectiveness Test |
| API | Active Pharmaceutical Ingredient |
| APIREG | API registration |
| CAPA | Corrective Action and Preventive Action |
| CBER | Center for Biological Evaluation and Research |
| CCP | Critical Control Points |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CFSAN | Center for Food Safety and Applied Nutrition |
| CF | Cystic Fibrosis |
| CFU | Colony Forming Unit |
| CP | Control Parameters |
| GDP | Good Distribution Practice |
| GMP | Good Manufacturing Practice |
| cGMP | Current Good Manufacturing Practice |
| CVM | Center for Veterinary Medicine |
| EEA | Economic European Area |
| EMA | European Medicines Agency |
| EP | European Pharmacopoeia |
| EU | European Union |
| FMEA | Failure Mode Effects Analysis |
| FMECA | Failure Mode Effects, Critically Analysis |
| FDA | Food and Drug Administration |
| HACCP | Hazard Analysis and Critical Control Points |
| ICH | International Conference on Harmonization |
| IR | Integrity and Recalls |
| ISO | International Organization Standardization |
| J&J | Johnson & Johnson |
| JP | Japanese Pharmacopoeia |
| MIA | Manufacturing and Importation Authorization |
| MET | Microbial Enumeration Tests |

| | |
|---|---|
| MHRA | Medicines & Healthcare products Regulatory Agency |
| MRA | Medicines Regulatory Agencies |
| MPN | Most Probable Number |
| NC | Non-conformities |
| NAI | No Action Indicated |
| OAI | Official Action Indicated |
| OC | Office of Compliance/Immediate Office |
| ODS | Office of Drug Security |
| OMQL | Office of Manufacturing Quality Letters |
| OOS | Out of Specification |
| OPDPL | Office of Prescription Drug Promotion Letters |
| OSIL | Office of Scientific Investigations Letters |
| PHA | Preliminary Risk Analysis |
| *Psa.* | *Pseudomonas sp.* |
| QbD | Quality by Design |
| QRM | Quality Risk Management |
| RRI | Risk-Ranking Index |
| RPR | Risk-Priority Rank |
| STP | Stability Test Programs |
| *Sta.* | *Staphylococcus sp.* |
| *Salm. Spp.* | *Salmonella sp.* |
| TAMC | Total Aerobic Microorganism Count |
| TBC | Total Bacterial Count |
| TSM | Tests for Specified Microorganisms |
| TYMC | Total Yeast and Mold Count |
| UK | United Kingdom |
| USA | The United States of America |
| USP | United States Pharmacopoeia |
| VAI | Voluntary Action Indicated |
| WLs | Warning Letters |
| WDA | Wholesale Distributor Authorisation |

# 1 Introduction

Microbiological Contamination of drug products is a significant risk for patient's health. The presence of microorganisms may impact on product integrity, pharmacological effects and therapeutic adherence (1). In many cases, depending on the route of administration, contaminated drug products may endanger the patient's life (2). In the literature, it is possible to find many cases of disease outbreaks associated with microbiological contamination of drug products. One of the most infamous and well known pharmaceutical incidents was the "Evans Medical Disaster" in 1972, in which contaminated dextrose infusion caused serious injuries and coast the life of five people, or the “tetanus infections of new-born babies” an outbreak disease that was associated with contaminated talc dusting powder. (2) (3) (4)

In fact, microbial contamination of non-sterile drug products began to be a concern in the 1960’s when *Kallings* et al. (1966) associated cases of salmonellosis to contaminated thyroid capsules. Since that time, microbiological contamination represents a challenge for the pharmaceutical industry and for regulatory agencies that had to require stricter microbial quality control standards. (2) (3)

Currently, microbiological contamination is one of the top ten causes responsible for drug product recalls in the United States of America (USA) and United Kingdom (UK) markets. According to Deborah Grady (2012) at least once per month, clinically relevant drug products are recalled from USA market, most of them are distributed nationwide or beyond, which may exacerbate the situation. (5)

Scott Sutton (2012) reviewed all recalls related to drug products and healthcare products registered by the Food and Drug Administration (FDA) database between the years 2004-2011. During this period were recorded 642 Recalls involving microbiological incidents and 22% concerned non-sterile drug products. Another important finding was that a large number of recalls (total of 43), mentioned *Burkholderia cepacia* as the microorganism responsible for the contamination and 23 recalls mentioned yeast and mold. (5)

*B. cepacia* represents a danger to patient health and safety. This bacterium is an opportunistic pathogen and constitutes a problem for immune-compromised patients, especially those afflicted with cystic fibrosis (CF). Although fungi rarely cause disease outbreaks, they represent an equal risk to immune-compromised patients and must also be controlled. (7) (8)

Beyond the consequences for the patients and their health, drug products recall, mainly associated with microbiological contamination, may damage a company's reputation and significantly impact the profitability and sales causing problems of high

proportions (8). Recently, Johnson & Johnson (J&J) had to recall from the market some drug products due to quality failures. Successive recalls occurred during 2010 and 2011 showing that J&J had frequent and urgent problems directly related to manufacturing and quality control. As a result, J&J temporary closed the Fort Washington plant (Pennsylvania, USA), reduced $1.2 billion in sales compared with 2009, and had to solve problems with USA courts. (10)

To control and reduce the microbial risks inherent to manufacturing process, the industries must implement strict process controls and follow to the letter the current Good Manufacturing Practice (cGMP).

As reported by Scott Sutton (2007), a significant challenge faced by non-sterile drug products manufacturers is the lack of information and contamination control programs. "*The sterile production facility knows there is a problem with contamination of batches, the non-sterile facility has a great temptation to believe they are not touched by these issues*" (11).

A question frequently raised by non-sterile manufacturers is what degree of microbial levels they must accept and how to control them. In this case, a science and risk-based approach may be useful to answer these questions and solve this issues. The ability to knowing all the hazards inherent to manufacturing process supports decision-making. In this way, a Quality Risk Management (QRM) is crucial to improving quality and reduce microbiological contamination. (12)

The microbiological risk analysis devoted to non-sterile drug products must take into account at least four considerations, such as (1) the intended use of drug product, as regards the dosage form and route of administration; (2) the identity and specificity of microorganisms responsible for contamination; (3) the product's characteristics, as regard the composition and formulation; (4) the potential impact on the population who takes the drug products (13) (14).

In addition, to facilitating decision making, QRM allows a better use of resources and a better awareness of cause and effect of the hazards (15). Identifying, quantifying the risk and prioritizing mitigation actions is a time-saving and cost-saving practice since a microbiologically related recall is an expensive process that goes beyond the direct costs and may damage the company's reputation, besides to endangering patient's life. (10)

## 1.1 Goals

In this context, the present work has the following three main goals, which are closely linked:

- Evaluating the occurrences and root causes of microbiological contamination in non-sterile drug products traded in the USA and the UK markets.
- Evaluating the microbial hazards involved in the manufacturing process and applying QRM principles to depict and quantify relevant risks.
- Providing science-based information to support decision-making and allow prioritizing mitigations actions by manufacturers.

## 1.2 Scope of the Dissertation

This work describes the development of a documentary analysis and a microbiological risk assessment. It provides information about microbiological contamination occurrence and the microbial hazards inherent to manufacturing process of non-sterile drug products. The work was accomplished in three stages. First, risk identification was conducted basing on information available in regulatory agencies databases, such as recalls and warning letters (WLs). Second, QRM tools as Pareto Chart, Ishikawa Diagram, Preliminary Risk Analysis (PHA) and Failure Mode Effects, Critically Analysis (FMECA) were used with the purpose of define risk factors and quantify the risk level. Lastly, a Risk-Ranking Index (RRI) and a Risk-Priority Rank (RPR) was developed to prioritizing mitigation activities and providing information to the manufacturer of non-sterile drug products.

## 1.3 Research Methodology

A documentary research was conducted to collect data and develop this study. The period analysed was between 2008 to February of 2016. The sorts of information investigated were reports of microbiologically related recalls and WLs addressed to the manufacturer of non-sterile drug products. Public databases made available by regulatory agencies, such as FDA, Medical Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA) were consulted. Data processing was carried out through QRM tools such as Pareto Chart, Ishikawa Diagram, PHA, and FMECA. The following sections explain in detail the methodology used in this work, which is summarized in Table 1, including the outputs obtained.

*Table 1: Summary of research methodology used and the outputs obtained in this work.*

| Reports registered between 2008 and February 2016 | | |
|---|---|---|
| | **Recalls** | **Warning Letters** |
| **Databases consulted** | FDA Enforcement Reports<br>MHRA Drug Safety Update | FDA Warning Letters<br>EMA EudraGDMP |
| **QRM tool used** | Pareto Chart | Ishikawa Diagram<br>PHA<br>FMECA |
| **Outputs** | Root causes for non-sterile drug products recalls<br>The relevance of microbiological contamination for recalls of non-sterile drug products<br>Root causes for microbiological contamination<br>Most cited microorganisms | Non-conformities (NC) by the manufacturer of non-sterile drug products.<br>Likelihood of occurrence of NC<br>Microbial hazards involved in manufacturing process<br>Risk-Ranking Index<br>Risk-Priority Rank |

### 1.3.1 Recalls

Recalls were investigated to study the occurrence of microbiological contamination of non-sterile drug products and the possible root causes of contamination. The flowchart below (Figure 1) illustrates all steps took to obtain data of microbiologically related recalls of non-sterile drug products.

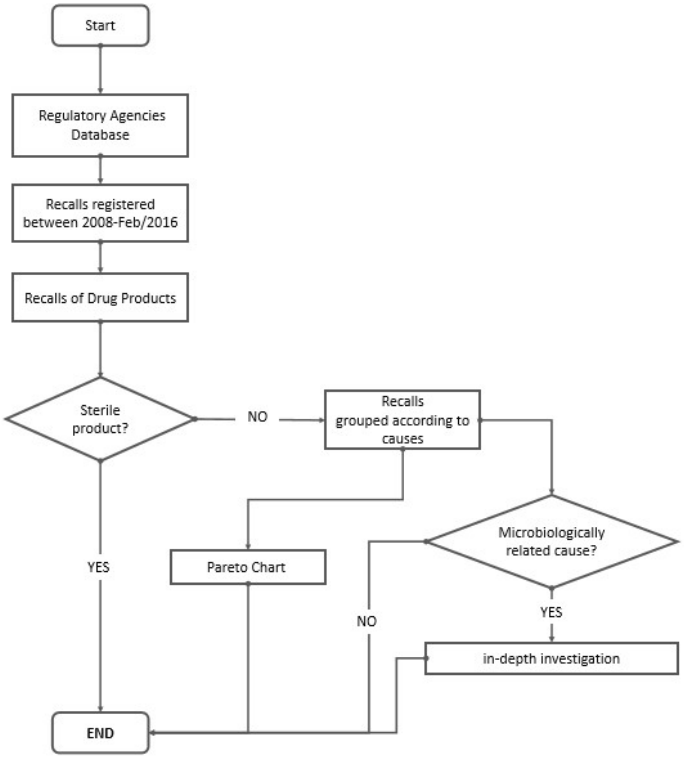



*Figure 1: Process flow of the documentary analysis of recalls*

#### 1.3.1.1 *Databases*

Two relevant databases were consulted to collect data from recall: the "FDA Enforcement Report" (16) and the "MHRA Drug Safety Update" (17). Recall data reflect the pharmaceutical markets from USA and UK.

##### 1.3.1.1.1 FDA Enforcement Report

The FDA Enforcement Report contains all recalls monitored and classified by the agency. This database is organized to provide weekly Enforcement Reports of recalled products in the following categories: *Biologics, Cosmetics, Devices, Drugs, Food, Tobacco* and *Veterinary*. In this work only the reports concerning Drugs were investigated. These category groups are over-the-counter and prescription drugs, as well as the other products not considered medicines, such as toothpaste, antiperspirants, dandruff, shampoos, and sunscreen. (16)

Some limitations inherent to the database are related to the register of recalls and the time of classification that is different from the time of recall. As the database registers the recalls by numbers, a specific recall may pertain to one batch or several batches. This work considers only the impact of the recall, rather than the number of batches recalled. Regarding the period, all recalls monitored by FDA are classified into categories (as mentioned above). Once classified, they are weekly registered in Enforcement

Report. In practice, this means that the date recorded in Enforcement Reports is different from the date of registration in FDA. This work considers the period of registration in the Enforcement Report.

#### 1.3.1.1.2 MHRA Drug Safety Update

The Drug Safety Update contains alerts and recalls of drug and medical devices monitored by the MHRA. This database is publicly available on the agency's website, and researchers can access monthly information. Alerts and recalls are classified into four categories, as follows: *Drug Alert*, *Medical device alert*, *Field safety notice*, and *Drug alert: company-led*. This work used data collected at Drug alert and Drug alert: company-led to conduct the research. (17)

As the MHRA Drug Safety Update has the same limitations as the FDA Enforcement Reports, the same considerations were herein applied.

### 1.3.1.2 *Pareto Chart*

Recalls collected in both databases, FDA, and MHRA, have a brief description of the problem, allowing identifying and grouping the causes to quantify their occurrence. The subsequent step was to organize the reasons in a descending order of occurrence and calculate their cumulative frequency to develop the Pareto Chart. This type of chart was used as a support statistical QRM tool, with the purpose to highlight the most important causes and analyse the respective contributions to recalls of non-sterile drug products.

## 1.3.2 Warning Letters

WLs were analysed to collect all violations in GMP identified by auditors during inspections. The violations or non-conformities (NC) indicate the failures committed by companies and may be caused by microbiological contamination recalls. This relationship was investigated by examining only WLs intended to the manufacturer of non-sterile finished products, with the purpose to identify failures made by this specific group of industry. All NC carried out by manufacturers were collected, examined and grouped by type of cGMP violation. This grouping allows establishing the likelihood of occurrence. The flowchart below (Figure 2) illustrates all steps carried out to obtain data from WLs issued to a manufacturer of non-sterile drug products.

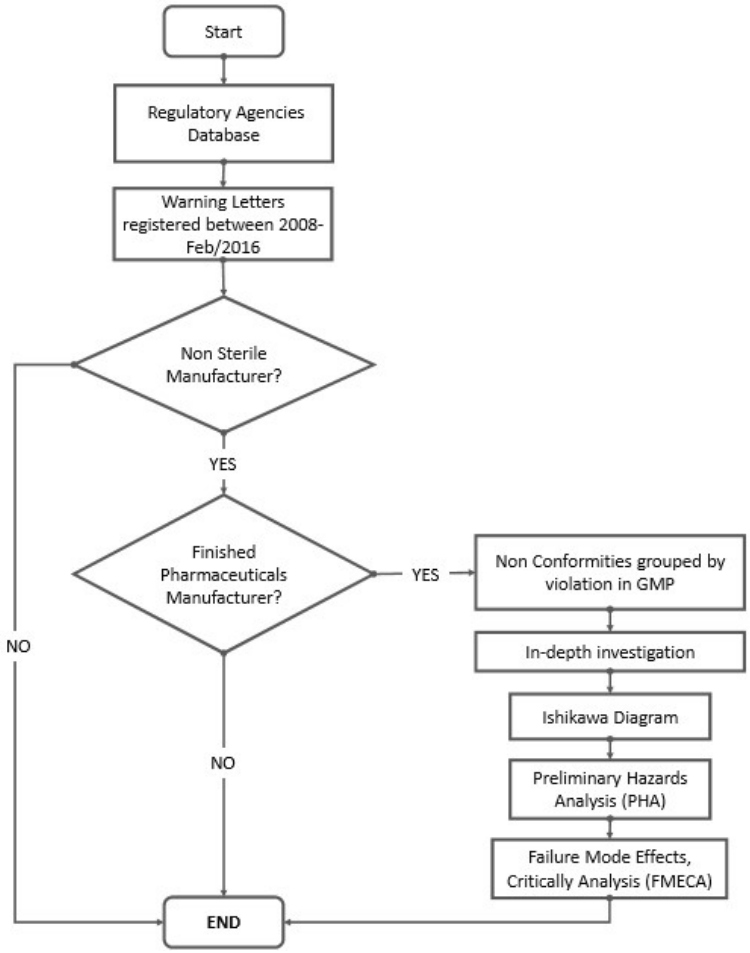



*Figure 2: Process flow of the documentary analysis of Warning Letters.*

### 1.3.2.1 *Databases*

WLs were collected from the FDA (18) and EMA-EudraGDMP (19) database. Data obtained reflects the reality of pharmaceutical industries under the jurisdiction of both agencies. Regulatory authorities within the Economic European Area (EEA), such as MHRA, have access to EMA – EudraGMDP, so that, this database contains information derived from regulatory authorities of countries belonging to the EEA.

#### 1.3.2.1.1 FDA Warning Letters

The FDA WLs database include letters issued to different sorts of industries, and it is organized by "Centers of Evaluation" such as: *Center for Biological Evaluation and Research* (CBER), *Center for Drug Evaluation and Research* (CDER), *Center for Devices* and *Radiological Health* (CDRH), *Center for Food Safety and Applied Nutrition* (CFSAN) and *Center for Veterinary Medicine* (CVM). In this work only the WLs supplied by the CDER were examined.

The WLs provided by CDER are available by years (1998-2016) and by "Office of prescription", as follows: *Office of Prescription Drug Promotion Letters* (OPDPL), *Office of Compliance/Immediate* (OC), *Office of Manufacturing Quality Letters* (OMQL), *Office of Scientific Investigations Letters* (OSIL), *Office of Drug Security* (ODS), *Integrity and Recalls* (IR). As the aim of this work is to investigate the harms microbiologically related to manufacturing of non-sterile drug products, the analysed WLs were those present in the OMQL. (18)

#### 1.3.2.1.2 EMA – EudraGMDP

The EudraGMDP database is a tool that contains complete information on pharmaceutical issues. It includes information on Manufacturing and Importation Authorizations (MIA) and Good Manufacturing Practice (GMP) certificates for authorized sites in the EEA and information on GMP certificates for manufacturers in third countries.

A GMP certificate or a WL is issued to a manufacturer by the competent national authority that carried out an inspection. If the inspectors conclude that the manufacturer does not comply with the statement of GMP, a WL is issued to the company. The WL may be issued to manufacturers of products inside and outside of the European Union, and all the letters are recorded into EudraGMDP.

EudraGMDP is organized into five categories such as *Manufacturing and Importation Authorisation* (MIA), *Compliance with Good Manufacturing Practice* (CGMP), *API Registration* (APIREG), *Wholesale Distributor Authorisation* (WDA) and *Good Distribution Practice Compliance* (GDP). The present work analyses the information provided by cGMP, which contains non-compliance reports. (19)

### 1.3.2.2 *Ishikawa Diagram*

An Ishikawa Diagram was used to analyse possible causes related to microbiological contamination of non-sterile products. All NC identified in FDA and EMA WLs were classified into 6Ms categories, as follows:

- Materials
- Machinery
- Mother Nature
- Man Power
- Measurements
- Methods

All NC were analysed without screening. The second step conducted, was to evaluate specific problems as root causes of contamination identified in Recalls. The

purpose of this step was to study the relation between root causes of recalls and failures by the manufacturer.

### 1.3.2.3 *Preliminary Hazard Analysis (PHA)*

The PHA was conducted with the cooperation of a sample of 14 representatives of the Portuguese pharma companies, within the framework of Projecto ISO/INFARMED (20) (herein called ISO committee).

Each member of the ISO committee classified the NC according to severity and likelihood of occurrence of the violation in their company. Three categories were used: low, moderate and high (Table 2). Risks were defined as the combination of likelihood of occurrence and severity of harm, the risk scale is shown in Table 3 and Table 4.

*Table 2: Quantitative evaluation of severity and likelihood of occurrence using three levels. Source (15)*

| Evaluation | Likelihood of Occurrence | Severity |
|---|---|---|
| **High** | The failure/accident occurs **Frequently** | The consequences of the failure/accident are **Important** |
| **Moderate** | The failure/accident occurs **Periodically** | The consequences of the failure/accident are **Moderate** |
| **Low** | The failure/accident occurs **Rarely** | The consequences of the failure/accident are **Low** |

*Table 3: Quantitative evaluation of risk*

| Risk Classification | | Severity | | |
|---|---|---|---|---|
| | | **Low (Rank 1)** | **Moderate (Rank 3)** | **High (Rank 5)** |
| **Occurrence** | **Low (Rank 1)** | 1 | 3 | 5 |
| | **Moderate (Rank 3)** | 3 | 9 | 15 |
| | **High (Rank 5)** | 5 | 15 | 25 |

*Table 4: Risk Classification*

| Risk Classification | |
|---|---|
| **Low** | 1-3 |
| **Moderate** | 5-9 |
| **High** | 15-25 |

For comparison purposes, two different RRI were developed, one using the likelihood defined by ISO committee's expertise and the other one using the likelihood of occurrence found in WLs issued by FDA and EMA. Table 5 illustrates the scale of frequency adopted to classify the NCs found in WLs as low, moderate and high.

*Table 5: Likelihood of occurrence scale using frequency found in FDA letters*

| Likelihood of occurrence | |
|---|---|
| **Low (Rank 1)** | 1 to 3% |
| **Moderate (Rank 2)** | 4 to 6% |
| **High (Rank 5)** | More than 7% |

### 1.3.2.4 *Failure Mode Effects, Critically Analysis*

As a second QRM tool used in this work, FMECA was applied to develop an RPR and highlight the most significant risks. The inclusion of "difficulty of detection" as a third parameter allows determining which risks should receive more attention.

ISO group also defined the difficulty of detection. The group classified each NC into three levels, “Low, Moderate and High” (Table 6). The RPR was obtained as the combination of the three risk factors. Table 7 and Table 8 summarize the combination and the outputs.

*Table 6: Quantitative evaluation of severity, the likelihood of occurrence and difficulty of detection using three levels. Source (15)*

| Evaluation | Likelihood of Occurrence | Severity | Difficulty of Detection |
|---|---|---|---|
| **High** | The failure/accident occurs **Frequently** | The consequences of the failure/accident are **Important** | The failure/accident **Will very likely not be detected** |
| **Moderate** | The failure/accident occurs **Periodically** | The consequences of the failure/accident are **Moderate** | The failure/accident **Might be detected** |
| **Low** | The failure/accident occurs **Rarely** | The consequences of the failure/accident are **Low** | The failure/accident **Will very likely be detected** |

*Table 7: Combination of the risk factors*

| Risk Classification | | Difficulty of Detection | | |
|---|---|---|---|---|
| | | Low (Rank 1) | Moderate (Rank 3) | High (Rank 5) |
| Low | 1 | 1 | 3 | 5 |
| | 3 | 3 | 9 | 15 |
| Moderate | 5 | 5 | 15 | 25 |
| | 9 | 9 | 27 | 45 |
| High | 15 | 15 | 45 | 75 |
| | 25 | 25 | 75 | 125 |

*Table 8: FMECA Risk-Priority Rank*

| FMECA Risk-Priority Rank | |
|---|---|
| 3rd Priority | 1-9 |
| 2nd Priority | 15-27 |
| 1st Priority | 45-75 |

## 1.4 Structure of the Thesis

This work is organized into five chapters, which address all of the issues relevant to microbiological contamination of non-sterile drug products such as standards and Pharmacopoeia tests, the QRM tools and principles, the results obtained with the documentary research, the RRI, the RPR and some suggestions on mitigations actions and the conclusion about this work.

**Chapter one** is a brief introductory chapter. It makes a general approach regarding microbiological contamination in drug products, the consequences to patients and pharmaceutical industry, and a risk-based approach as a possible solution to reduce the problem. This chapter also presents the goals, the scope and the research methodology used in this work.

**Chapter two** is the literature review. This chapter is a critical summary of published material, standards, Pharmacopoeia microbiological tests, regulatory issues, inspections, recalls, WLs and QRM principles and tools. It includes all the relevant information necessary to evaluate the microbiological contamination of non-sterile drug products.

**Chapter three** contains all the results obtained in this work. The research findings and the risk evaluation are presented in detail and separately as tables and bar charts. To facilitate the comprehension results are shown according to the database and pharma market under study.

**Chapter four** is the discussion of the results obtained. In this section, the relevant findings are discussed in detail. Each pertinent information achieved with the documentary analysis and the main observations about microbiological contamination of non-sterile drug products are reviewed. The root causes responsible for recalls and most frequent failures by the manufacturer are thoroughly examined.

**Chapter five** contains the final conclusions and summarizes the results obtained, as well the risks associated with the manufacturing process. Also, future work for the present application is suggested to obtain more detailed information.

# 2 Literature Review

This chapter aims to review the microbiological control tests required by legislation, a general approach to QRM principles and tools, and a review of the relevant, specific literature. It is divided into two main sections. The first section deals with microbial control, standards, Pharmacopoeia tests and legislation issues. The second section deals with the QRM principle and most used tools.

## 2.1 Microbiological Contamination

The first requirements for testing non-sterile drug products for microbial quality appeared on 1942 in United States Pharmacopoeia (USP), the XII edition introduced the test “Bacteriological Examination of Gelatin”. Despite this test, most non-sterile drug products were not required to be assessed for microbial quality (21). Only in the 1960’s these quality attributes began to be a concern and a prominent issue. On the occasion, studies carried out by Swedish National Board of Health has revealed a high level of microbial contamination after drug products manufacturing and disease outbreaks were connected with microbiological contamination of tablets and capsules (2). These studies opened the road for development of stricter microbial quality control standards and in 1970 USP XVIII introduced the chapter "Microbiological attributes of non-sterile pharmaceuticals" and microbial quality control became a requirement. (21) (22) (23)

Currently, USP presents three chapters related to microbiological control testing and devoted to non-sterile drug products <61>, <62> and <1111> and 1 chapter related to antimicrobial effectiveness tests <51> (24). All tests present in these chapters were harmonized with the European Pharmacopoeia (EP) and Japanese Pharmacopoeia (JP) in 2007. Table 9 lists the pharmacopoeial tests equivalent in USP, EP, and JP. (25) (26) (27)

Chapter <1111> in USP and chapter 5.1.4 in EP are offered as information guidance. Other chapters present in Table 9 contain reference tests that are enforceable by regulatory agencies. (27) (28)

*Table 9: Pharmacopeia harmonization: equivalence of microbiological tests. Source (27)*

| United States Pharmacopoeia | Japanese Pharmacopoeia | European Pharmacopoeia |
|---|---|---|
| *<51> Antimicrobial Effectiveness Testing* | *JP 16 G4 Microorganisms: preservatives-effectiveness tests* | *5.1.3 Efficacy of antimicrobial preservation* |
| *<61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* | *JP chapter 16 4.05. I Microbiological examination of non-sterile products: total viable aerobic count* | *2.6.12 Microbiological Examination of non-Sterile Products: Microbial Enumeration Tests* |
| *<62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* | *JP chapter 16 4.05. II Microbiological examination of non-sterile products: tests for specified micro-organisms* | *2.6.13 Microbiological Examination of non-Sterile: Tests for Specified Microorganisms* |
| *<1111> Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* | - | *5.1.4 Microbiological Quality of non-sterile Pharmaceutical Products* |

### 2.1.1 Standards and acceptable criteria

The standards directed to non-sterile drug products are based on acceptance criteria such as the concentration of organism that may be present and the absence of specific and potentially hazardous ones. Another important requirement for non-sterile drug products is the presence of preservatives. Antimicrobial preservatives are necessary to protect the drug products from microbiological growth and contamination. (29) (30)

The following sections introduce the required Pharmacopoeial tests as well as the acceptance limits for microbial presence in non-sterile drug products. These sections discuss EP and USP mandatory tests such as the Antimicrobial Effectiveness Tests (AET), Microbial Enumeration Tests (MET) and Tests for Specified Microorganisms (TSM).

#### 2.1.1.1 *Antimicrobial Effectiveness Tests*

Preservatives are excipients added in a multi-dose formulation with the purpose to inhibit microbial contamination. However, it should be noticed that the inclusion of preservatives - always at the lowest feasible concentration - needs special justification because the use of these substances should be avoided whenever possible, particularly in the case of pediatric formulations (31) (32) (33). In other words, antimicrobial preservatives must be used in a concentration that is effective but non-toxic to patients,

on no account should they be used as an alternative to GMP (31). For these reasons, the inclusion of any antimicrobial preservative in a pharmaceutical formulation must be entirely justified, including the concentration used, the proof of safety and efficacy, the method of control in the drug product, the levels of storage of breached and unbreached containers and details on the labelling of the medicinal product (31).

The AET is performed by adding high concentrations of specific microorganisms to the preservative-containing product with the purpose to simulate a contamination. The inoculated samples are incubated at 20°C to 25°C and watched during 28 days. During pre-defined periods, the microorganisms are counted with the purpose to determine any change or growth. (32) (33)

Preservative effectiveness acceptance criteria represent the major difference between USP and EP. Pharmaceutical products are divided into four categories based on the product risk and criticality of the preservative system as shown in Table 10. The categories determine the acceptance criteria. Although an important test, the AET is not a routine batch release test. Table 11, shows the difference between criteria adopted by EP and USP. (33) (34) (35)

Usually, five microorganisms are used as a challenge in AET, like *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans* and *Aspergillus niger*. The EP do not include *E. coli* in the test, although allowing supplementing with additional species. (32)

#### 2.1.1.2 *Microbial Enumeration Tests*

The presence of a microorganism in drug products has many negative impacts. This sort of contamination may cause a degradative effect, inactivation of the therapeutic activity and changes in organoleptic characteristics of drug products (2). In this line, standards are required for establishing a limit or acceptable criteria of microbial presence in non-sterile products.

Acceptable criteria for non-sterile drug products are based upon the Total Aerobic Microbial Count (TAMC) and the total combined Yeast/mold count (TYMC). After the growth test, the microbial recovery is enumerated by one of 3 prescribed methods: Membrane Filtration, Plate Count and Most Probable number (MPN). Microbiological test methods are highly variable and must be validated by the industry. (36) (37)

Acceptance criteria are based on individual results or the average of replicate counts when these are performed. Table 12 shows the acceptance limits for each dosage form established by International Pharmacopoeia and harmonized with USP, EP, and JP. (38)

*Table 10: Categories of drug products and USP specifications for antimicrobial efficacy. Source (32)*

| Category | Product Description | Criteria for bacteria | Criteria for Yeast and Mold |
|---|---|---|---|
| 1 | Parenteral preparations (injections and emulsions)<br><br>Ear preparations, eye preparations and sterile nasal preparations (in aqueous base) | ≥1.0 log reduction at day 7 relative to initial count<br><br>≥3.0 log reduction at day 14 relative to initial count<br><br>No increase at day 28 relative to day 14 count | No increase at days 7, 14, and 28 relatives to initial count |
| 2 | Cutaneous preparations (in aqueous base), non-sterile nasal preparations, non-sterile emulsions Products for mucosal application | ≥2.0 log reduction at day 14 relative to initial count<br><br>No increase at day 28 relative to day 14 count | No increase at days 7, 14, and 28 relatives to initial count |
| 3 | Oral products in aqueous base (excluding antacids) | ≥1.0 log reduction at day 14 relative to initial count<br><br>No increase at day 28 relative to day 14 count | No increase at days 7, 14, and 28 relatives to initial count |
| 4 | Antacids in aqueous base | No increase at days 14 and 28 relatives to initial count | |

*Table 11: Acceptance criteria - the difference between EP and USP. Source (33)*

| Categories Groups | Inoculation | $Log_{10}$ Reduction | | | | | |
|---|---|---|---|---|---|---|---|
| | (CFU) | 6Hr | 24Hr | 7 Days | 14 Days | 21 Days | 28 Days |
| USP: Bact. | $10^5$-$10^6$ | - | - | 1.0 | 3.0 | - | NI |
| EP-A: Bact. | $10^6$ | 2 | 3 | - | - | - | NR |
| EP-B: Bact. | $10^6$ | - | 1 | 3 | 1 | 1 | NI |
| USP: Yeast | $10^5$-$10^6$ | - | NI | NI | NI | NI | NI |
| EP-A: Yeast | $10^6$ | - | 2 | - | - | - | NI |
| EP-B: Yeast | $10^6$ | - | - | 1 | - | - | NI |
| USP: Mold | $10^5$-$10^6$ | - | NI | NI | NI | NI | NI |
| EP-A: Mold | $10^6$ | - | 2 | - | - | - | NI |
| EP-B: Mold | $10^6$ | - | - | 1 | - | - | NI |

*Table 12: TAMC and TYMC acceptable criteria of the International Pharmacopoeia. Source (38)*

| Dosage form | TAMC (CFU/g or CFU/ ml) | TYMC (CFU/g or CFU/ ml) |
|---|---|---|
| Non-aqueous oral preparations | $10^3$ | $10^2$ |
| Aqueous oral preparations | $10^2$ | $10^1$ |
| Rectal preparations | $10^3$ | $10^2$ |
| Oromucosal, gingival, cutaneous, nasal and auricular preparations | $10^2$ | $10^1$ |
| Vaginal preparations | $10^2$ | $10^1$ |
| Transdermal patches (limits for one patch including adhesive layer and backing) | $10^2$ | $10^1$ |
| Preparations for inhalation (special requirements apply to liquids preparations for nebulization) | $10^2$ | $10^2$ |
| Oral dosage forms, other than herbal medicines, containing raw materials of natural origin for which antimicrobial pre-treatment is not feasible and the relevant national or regional authority accepts TAMC of the raw material exceeding 103 CFU/g or CFU/mL | $10^4$ | $10^2$ |

### 2.1.1.3 *Tests for Specified Microorganisms*

Tests for specific microorganisms were designed to detect the presence of indicator microorganisms named "objectionable organisms." These organisms are defined according to the route of administration and can be *P. aeruginosa, S. aureus*, *Salmonella enterica, E. coli, C. albicans* and bile-tolerant gram-negative bacteria. (25) (29) (38)

Selective culture media, defined by the pharmacopoeias, are used to determine the presence/absence of target species. The microbiological test methods are highly variable and must be validated by the industry (39) (40). Table 13 shows the objectionable organisms defined by dosage form. EP, USP, and JP harmonized these criteria. (25) (38)

*Table 13: Objectionable organisms by dosage form. Source (29) (38)*

| **Route of administration** | **Absence of specific microorganism(s) (1G or 1 mL)** |
|---|---|
| Non-aqueous oral preparations | *E. coli* |
| Aqueous oral preparations | *E. coli* |
| Rectal preparations | Non-designed |
| Oromucosal, gingival, cutaneous, nasal and auricular preparations | *S. aureus*<br>*P. aeruginosa* |
| Vaginal preparations | *P. aeruginosa* |
| Transdermal patches (limits for one patch including adhesive layer and backing) | *S. aureus*<br>*P. aeruginosa*<br>*C. albicans* |
| Preparations for inhalation use (special requirements apply to liquid preparations for nebulization) | *S. aureus*<br>*P. aeruginosa*<br>Bile-tolerant gram negative bacteria |
| Oral dosage forms, other than herbal medicines, containing raw materials of natural origin for which antimicrobial pre-treatment is not feasible and the relevant national or regional authority accepts TAMC of the raw material exceeding 103 CFU/g or CFU/mL | Non-designated |

## 2.1.2 Sources of microbial contamination

To reduce and control the existence, growth and multiplication of microorganism in a pharmaceutical facility it is necessary better understand the root causes and potential sources of contamination. Conventional reservoirs of microorganisms are raw material, production atmosphere, persons that conduct the process, equipment, and the

container into which products are filled and sealed. These risk factors were classified in descending order of importance, as follow: (2) (41)

1. Ingredient water
    a. Pharmaceutical ingredients
    b. Process equipment
    c. Manufacturing personnel
    d. Manufacturing environment

Although these risks are well known, each industry, process and product have its peculiarities and microflora that should be thoroughly studied. To minimize microbiological contamination, pharmaceutical manufacturers must work under specified conditions as defined by GMP and should implement a risk-based approach to improving quality and support decision-making. (2)

A robust and well-designed facility and process control are crucial to limit the growth and spread of microorganisms. Figure 3 illustrates some of the process controls and microbiological quality controls required by regulatory agencies. (2) (42)

#### 2.1.2.1 *Environmental Monitoring*

Environmental monitoring and control programs devoted to non-sterile drug products are unclear issues. Manufacturers frequently ask what degree of microbial control is required for non-sterile drug products and what level of contamination is compatible with patient safety. Limited or excessive controls are undesired. When used in excess and without specific reasons, the microbiological control is not advantageous because it may increase the costs to the manufacturer (41).

USP <1115> Bioburden Control of Non-Sterile Drug Substances and Products gives some orientation about microbiological control. This chapter provides recommendations for industry regarding control strategies, product development, routine manufacturing, equipment design and use, personnel training, manufacturing environment, as well as overall management of microbiological control programs. (41)

USP <1115> recommends a risk-based approach to design microbial control programs and select sites for monitoring. Areas of high personnel activity or with product exposure should frequently be checked, and mitigation actions should be developed based on the risk assessment. (41) The microbiological risk analysis devoted to non-sterile drug products must take into account the intended use of drug product, the identity, and specificity of microorganisms responsible for contamination; the product's characteristics and the potential impact on the population who takes the drug products (13) (14)

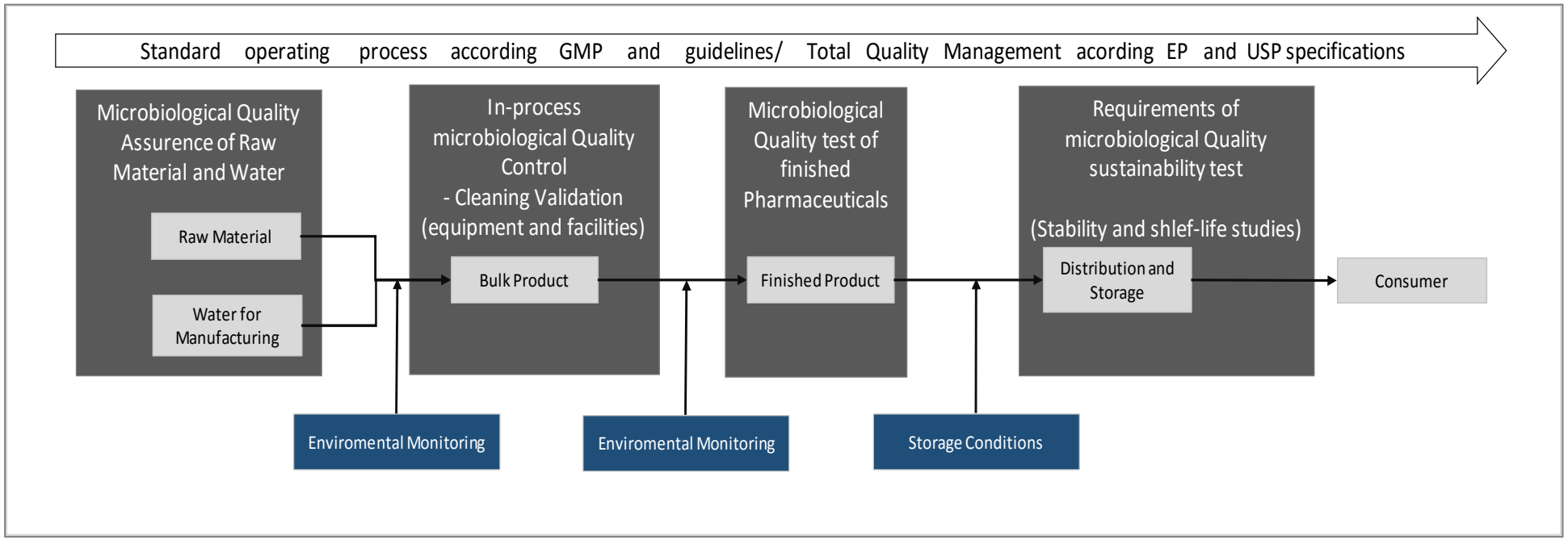



*Figure 3: Total maintenance scheme of the microbiological quality standards of drug products. Source (42)*

Although classified environments are not required for non-sterile product manufacturing, it may be a useful component in the overall microbiological control program. The World Health Organisation (WHO) recommends the use of cleanrooms classified as ISO 8 to manufacturing non-sterile drug products. Table 14 shows Clean rooms classification and acceptance level for microbiological presence on the air. (43) (44)

*Table 14: Cleanrooms classification. Source (45) (46)*

| **Max. Microbiological Active Air Action Level Colony Forming Units (CFU) per cubic meter (average values)** | | | | |
|---|---|---|---|---|
| **Grade** | | | **Limits** | |
| **ISO 14644** | **FDA** | **EU GMP** | **FDA (air sample CFU/m$^3$)** | **EU cGMP (air sample CFU/m$^3$)** |
| **5** | **100** | **A** | 1 | <1 |
| **6** | **1000** | **B** | 7 | 10 |
| **7** | **10000** | **C** | 10 | 100 |
| **8** | **100000** | **D** | 100 | 200 |

### 2.1.2.2 *Quality control of water used in pharmaceutical preparations*

Water is an important source of contamination of non-sterile drugs products and can be employed as part of the formulation or to final rinse of clean equipment. Therefore, the quality or type of water used should be chosen based on product risk. The flowchart (Figure 4) below illustrates many uses for water in pharmaceutical industry and shows the steps necessary to select the correct type of water for intended purposes. (47)

In this context, non-sterile drug products mainly require purified water and drinking water for the manufacturing process. Populations of Gram-negative bacteria and many fungi (mold and yeast) can grow in this kind of water (purified dechlorinated water). Thus, controls for microbial quality are important and should be applied for its various uses. Table 15 shows specifications and acceptable levels for parameters required for purified water quality assurance according to USP and EP. (47) (48)


*Figure 4: Water for pharmaceutical uses. Source (47)*

*Table 15: Purified water specification according to the USP and the EP. Source (48) (47)*

| Parameter | Unit | USP | EP. (Bulk) |
|---|---|---|---|
| TOC | ppm C | 0.50 | 0.50 |
| Conductivity | µS/cm 20°C | - | < 4.3 |
| Conductivity | µS/cm 25°C | < 1.3 | - |
| Nitrate (NO3) | ppm | - | < 0.2 |
| Heavy metals | ppm as Pb | - | < 0.1 |
| Aerobic bacteria | CFU/ml | < 100 | < 100 |

### 2.1.2.3 *Quality control of active pharmaceutical ingredients, in-process materials, and excipients*

Another important source of contamination is active ingredients, in-process materials and excipients used in drug formulations and manufacture. The greatest concerns are mainly the materials of natural origin and materials that have a high level of water activity. (41)

To ensure the microbial quality of raw materials, it is necessary to implement effectively and scientifically quality control tests and set suitable microbial limit standards for incoming raw materials and excipients. Each component, excipient, and Active Pharmaceutical Ingredient (API) should be tested for TAMC and TYMC and objectionable microorganism according to specific monographs. Table 16 and Table 17 show acceptable limits for microbial contamination in some of the excipients used in the formulation of drug products and required by USP and EP. (49)

*Table 16: USP microbial attributes for raw materials. Source (49)*

| | **Test for presence of** | | | | | |
|---|---|---|---|---|---|---|
| | **TAMC** | **TYMC** | ***Sta.*** | ***Psa.*** | ***E. coli*** | ***Salm. Spp.*** |
| **Materials** | **(CFU/g or mL)** | | **Presence/Absence test** | | | |
| Acacia | | | | | | X |
| Agar | | | | | | X |
| Alginic Acid | 200TBC | | | | X | X |
| Betadex | 1000 TBC | | | | X | X |
| Benzalkonium chloride solution (<5.0%) | | | | X | | |
| Caramel | | | | | X | X |
| Gelatin | 1000 TBC | | | | X | X |
| Lactose Monohydrate | 100 | 50 | | | X | |
| Mg Stearate | 1000 | 500 | | | X | X |
| Sodium alginate | 200 TBC | | | | X | X |
| Corn Starch (absorbable dusting powder) | 1000 | 100 | X | X | X | |
| Compressible sugar | | | | | X | X |
| Sugar Spheres | 100 | | X | X | X | X |
| Talc (topical administration) | 100 | 500 | | | | |
| Xanthan gum | | | | | X | X |

*Table 17: EP microbial attributes for raw materials. Source (49)*

| | Test for presence of | | | | | |
|---|---|---|---|---|---|---|
| | **TAMC** | **TYMC** | ***Sta.*** | ***Psa.*** | ***E. coli*** | ***Salm. Spp.*** |
| **Materials** | **(CFU/g or mL)** | | **Presence/Absence test** | | | |
| Acacia | $10^4$ | | | | X | |
| Agar | $10^3$ | | | | X | X |
| Alginic Acid | $10^2$ | | | | X | X |
| Betonite | $10^3$ | | | | | |
| Gelatin | $10^3$ | | | | X | X |
| Guar galactomannan | $10^3$ | | | | X | X |
| Lactose Monohydrate | $10^2$ | | | | X | |
| Maize starch | $10^3$ | $10^2$ | | | X | |
| Sodium alginate | $10^3$ | | | | X | X |
| Sodium starch glycolate (Types A and B | | | | | X | X |
| Talc (for oral administration) | $10^3$ | $10^2$ | | | | |
| Talc (for topic administration) | $10^2$ | $10^2$ | | | | |
| Tragacanth | $10^4$ | | | | X | X |
| Wheat starch | $10^3$ | | | | X | |

### 2.1.3 Consequences of a microbiological contamination

The industry expected to follow the letter cGMP requirements and maintain strict adherence to microbial contamination controls practice during manufacturing of pharmaceutical products, but it is not uncommon to see drug products being withdrawn from the market due to microbiological contaminations.

A sequence of actions can be taken by regulatory agencies to protect the consumer from quality deviations, such as inspections in manufacturing plants, warning letters, field alerts, recalls and in some cases injunction and penalties.

The following section describes the enforcement activities taken by regulatory agencies.

#### 2.1.3.1 *Inspections and audits*

There are different types of inspections such as pre-approval inspection, routine inspection, "for cause" inspections and “follow-up” inspections. "For cause" inspection happens with the purpose to investigate a particular problem that has come to agency’s attention, such as a recurrence of recalls and patient’s complaints. “Follow up” inspections happen with the purpose to verify if corrective actions have been taken.

Despite different sort of audits, the primary purpose of inspecting a pharmaceutical manufacturing plant is identifying NCs that could endanger patient's life and obtain correction of those deficiencies. (50)

Since 2009, FDA and EMA are involved in an interaction project; that aims to share resources and findings, reducing unnecessary international duplication of inspections, increasing the number of facilities inspected and further harmonizing regulatory requirements. Despite this project, there are many differences in the inspection policies adopted by FDA and EMA. Each agency has its methods and rules to perform an audit; Table 18 shows the main differences between FDA and EMA.(51) (52)

*Table 18: Differences in inspection between FDA and EMA. Source (51)*

| Inspection | FDA | EMA |
|---|---|---|
| Beginning of inspection | Form 482 with FDA signature and notice of inspection | Open discussion about the purpose, expectation, and the inspection |
| Regulatory Classification | 1. NAI- No action indicated<br>2. VAI- Voluntary action indicated<br>3. OAI- Official action indicated | 1. Critical<br>2. Major<br>3. Minor<br>4. Others |
| Closeout meeting | FDA inspectors present/issue all the significant problems, violations, objectionable conditions, etc. to the most responsible person in the firm on FDA-483 in writing. | Oral feedback, the inspector discusses all the organization's shortcomings and problems. |
| Request for documentation | During the inspection | Before inspection |

#### 2.1.3.2 *Warning Letters*

During an inspection all-important observations are registered by the auditor. If the findings are serious enough, a WL is issued to the company. This formal notification is one of the main tools used to inform industries of non-conformities and violations committed and allows for voluntary and prompt corrective action. If the company does not correct the problems identified within a period of time, subsequent actions may be taken by agencies as seizure, injunction, civil money penalties, prosecution. (18) (50)

Concerning the warning letters issued by FDA, each violation in cGMP committed by the manufacturer has its specific regulatory references cited in the document. The FDA requires a written response within 15 working days and, if the industry fails to comply, severe repercussions can be adopted. (18)

On the other hand, WLs issued by EMA have significant difference concerning structure. Contrary to FDA, violations in cGMP are not cited using specific regulatory references. All non-compliances identified are described in text form. The WLs present in EMA databases were reported by inspectors from several regulatory agencies of the member states of the European Union. In this way, the details found in the contents of WLs vary according to the agency policies. (19)

#### 2.1.3.3 *Drug product recalls*

A recall occurs when a drug product has a quality defect or is potentially harmful to the patient. The company responsible for the product can detect the problem and inform official authorities requiring a voluntary recall, or it can happen after authorities raised concerns about the product, after an inspection or after receiving some patient's complaints (53). Recalls vary in severity and in the actions that must be taken to protect the public health.Table 19 shows the classification of recalls implemented by the FDA and the MHRA. (54) (55) (56)

As reported by Meghan Lehmann (2010), there are three stages involving a drug product recall, as follows:

- Submission of the recall
- Public notification
- Evaluation of the recall process

Once a recall is defined as necessary, an immediate action is required. In addition to investigate the root causes of the problem, the companies should use a strategy able to broach the following crucial questions: the consequences of the recall, how they intend notifying patients about the recall, instructions for patients on what to do with the ongoing health treatment, and the process for returning affected product. (56) (57)

*Table 19: Recalls classification - FDA and MHRA. Source (54) (55)*

| FDA Recalls Classification | MHRA Recalls Classification |
|---|---|
| Class I: Includes a health hazard situation where there is reasonable possibility that the use of the product will lead to serious, adverse health consequences or death. | Class 1 requires an immediate recall because the product poses a serious or life-threatening risk to health. |
| Class II: Includes a potential health hazard situation where there is a remote possibility of adverse health consequences from the use of the drug product. | Class 2 specifies a recall within 48 hours because the defect could harm the patient but is not life threatening. |
| Class III recall: Includes a situation where the use of the drug product is not likely to cause adverse health outcome. | Class 3 requires action to be taken within 5 days because the defect is unlikely to harm patients and is being carried out for reasons other than patient safety. |
| Market withdrawal: When a product has a minor violation that would not be subject to FDA legal action “market withdrawal” occurs. The drug product is removed by the firm from the market or corrects the violation. | Class 4 alerts advise caution to be exercised when using the product but indicate that the product poses no threat to patient safety |

### 2.1.4 Quality Improvement

Many procedures can be adopted to avoid that contaminated drug products reach the consumers. A risk identified in the early stages of the process can prevent a future recall, possible damage to the company and especially to the patients. In this regard, a quality risk management is fundamental to improve quality and avoid those serious consequences. The flow chart below (Figure 5), illustrates possible damages a quality deviation can cause to a company and a patient. The sooner the failures are identified, the smaller will be the damage caused to the company and lower risk to the patient. (58)

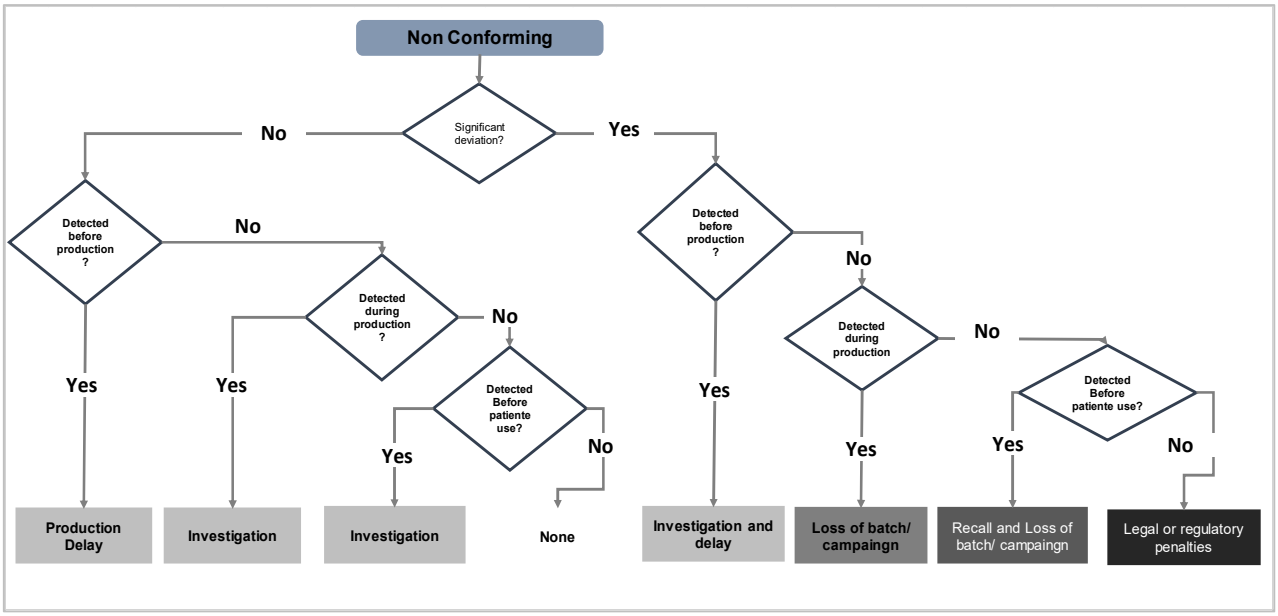



*Figure 5: Quality and business impact of non-conformities. Source (58)*

## 2.2 Quality Risk Management

Quality Risk Management is an important tool used by many industries to monitor, control and manage a different kind of hazards. In the pharmaceutical industry, since ICH-Q9 (12) has been published the use of QRM tools increased and industries and regulatory agencies have made significant efforts in this field. Many initiatives in cGMP are based on the ability to knowing all the hazards involved in the manufacturing process and to incorporate a science and risk-based approach to make decisions. In recent years, considerable emphasis on risk analysis was developed, leading the regulatory agencies to include these principles into their regulatory requirements. (59) (60)

The potential benefits and effectiveness of QRM implementation in the pharmaceutical industry are well documented and disseminated. It is possible to find in literature many case studies that illustrate the success obtained and the various applications of QRM principles and tools during all production process steps or product's life cycle. (61)

Despite visible progress, Kevin O'Donnell (2015) showed that many issues that industry had in 2005 are still present today and mentioned four key problems often seen in QRM process that obstruct its purpose as "Lack of good science, too little rigor in risk evaluation, poor management of knowledge and overuse of formal risk assessment" (60)

These common mistakes can be responsible for some failures observed in practice as microbiologically related recalls. Contrary to expectations, quality-related defects have increased during these years. This fact raises some doubt about the current

implementation of QRM tools and if the production process has been designed using a risk-based approach. (60)

### 2.2.1 Microbiological Quality Risk Management

Microbiological contamination is an issue often discussed in QRM. Many works have been published in this regard. In general, the studies address the product lifecycle, ranging from analysis of process design to storage of the finished product. (61)

Donald Singer (2014) reviewed all possible risks of microbiological contamination during drug product's lifecycle. His analysis indicates hazards and challenges inherent of each step of the process and fits all sort of pharmaceutical industries, including sterile and non-sterile. For the author, industry should pay more attention at the packing stage; he considers this step as the first line to prevent microbiological contamination. Another important issue that industry must be alerted is what happens after production when the finished products are in the warehouse. In this situation, environmental conditions are crucial to avoid microbiological proliferation. (62)

### 2.2.2 Quality Risk Management Principles

According to ICH-Q9, the risk is defined as the combination of the probability of occurrence of harm and severity of the harm. Quality Risk Management is a systematic process for the assessment, control, communication and review of risks. For ICH-Q9, management system should consider patient safety as the primary objective. (12)

The ICH Q9 proposed two principles to access QRM (12):

- *"Risk evaluation should be based on scientific knowledge and link to the protection of the patient; and"*
- *"The level of effort, formality, and documentation of the risk management process should be commensurate with the level of risk."*

The WHO, inspired by the ICH-Q9, published in 2010 a QRM guideline-directed to medicines regulatory authorities (MRA) and pharmaceutical industries, in which two more important points were added to the principles mentioned in the Q9 (63):

- *"When applied, processes using QRM methodologies should be dynamic, iterative and responsive to change;*
- *The capability for continual improvement should be embedded in the QRM process".*

The concept about QRM was illustrated in a Model proposed by the ICH-Q9 (12). The flowchart below shows all steps of the process involved in the management of risk. (Figure 6).

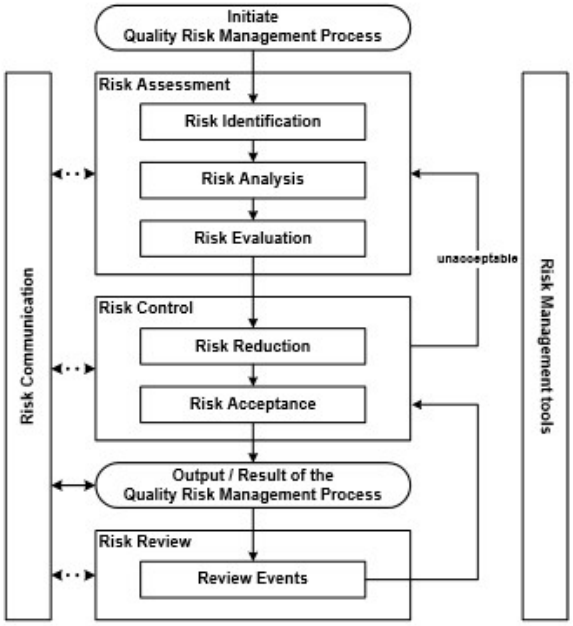



*Figure 6: Overview of a typical quality risk management process according to the ICH-Q9. Source (12)*

Once the problem is well understood and its causes and effects identified, it is possible to develop solutions and mitigations actions. An important accomplishment of this process is the selection of QRM tools. In this way, the main tools and principles used will be addressed in next topics. A great variety of techniques and tools have been developed and reported in the literature, the most widely adopted ones are presented below.

### 2.2.3 Quality Risk Management Tools

Several tools are available to support all the QRM phases. This section introduces the most used tools and discusses their benefits and limitations. Table 20 presents the QRM tools and their primary characteristics. (15)

In the next sections, the following tools for risk analysis will be addressed:

- Preliminary Hazard Analysis - PHA
- Failure Mode Effects Analysis and Failure Mode Effects, Critically Analysis- FMEA and FMECA
- Hazard Analysis and Critical Control Point - HCCP
- Fishbone (Ishikawa) Diagram
- Pareto Chart

*Table 20: Basic classification of tools used in QRM. Source (15)*

<table>
<tr><th colspan="5">Characteristics</th><th>Tools</th></tr>
<tr><td rowspan="8">Tools for Risk Analysis</td><td rowspan="8">Inductive/ single factors</td><td colspan="2">Basic/ informal</td><td>Simple Organization of data</td><td>Flowchart/ Process Map/ checklist/ Ishikawa Diagram (Fishbone diagram)</td></tr>
<tr><td rowspan="7">Formal</td><td rowspan="2">Identification of Hazards and their potential effects</td><td>Risk is not estimated</td><td>PHA (Preliminary Hazard Analysis)</td></tr>
<tr><td>Risk is estimated</td><td>PRA (Preliminary Risk Analysis)</td></tr>
<tr><td rowspan="2">Evaluation of failure modes and their potential effects</td><td>Risk is not estimated</td><td>FMEA (Failure Mode Effects Analysis)</td></tr>
<tr><td>Risk is estimated</td><td>FMECA (Failure Mode, Effects, and Critically Analysis)</td></tr>
<tr><td colspan="2">Evaluation and monitoring of Hazards</td><td>HACCP (Hazard Analysis and Critical Control Points)</td></tr>
<tr><td colspan="2">Analysis of deviation using “Keywords.”</td><td>HAZOP (Hazard Operability Analysis)</td></tr>
<tr><td colspan="2">Identification of real or potential problems</td><td>FTA (Fault Tree Analysis)</td></tr>
<tr><td colspan="5">Tools for risk comparison</td><td>Risk-Ranking and Filtering</td></tr>
<tr><td colspan="5">Supporting Statistical tools</td><td>Control Chart/ Design of experiments/ Histograms/ Pareto Chart/ Process Capability Analysis</td></tr>
</table>

### 2.2.3.1 *Preliminary Hazard Analysis – PHA*

PHA is a formal tool usually used in early stages of a QRM. It is considered the ideal tool to start the study because can be applied when information is limited (15) (64).

The ICH Q9 defines the PHA tool in a few steps, as follows (12):

- *“Identification of the possibilities that the risk event happens”;*
- *“Qualitative evaluation of the extent of possible injury or damage to health that could result”;*
- *“Relative ranking of the hazard using a combination of severity and likelihood of occurrence”;*
- *“Identification of possible remedial measures.”*

The results obtained with this technique consist of a list of risks that can be ordered by scores. The list can be presented as a table containing the hazards, the

causes, and possible measures designed to minimize the harm (15). In practice, final results range from recommendations about the process and requests for more detailed assessment. Usually, results obtained with PHA are further assessed with other CRM tools.(64)

According to with IEC/ISO 31010 (64) the PHA strengths include the possibility to use this tool when there are limited information and the option to consider its use at the beginning of the assessment. The limitation is that PHA provides only initial information.(64)

#### 2.2.3.2 *Failure Mode Effects Analysis (FMEA)*

Failure modes and effects analysis (FMEA) is a technique used to analyse the possible ways in which a process or system can fail (64). It is useful to determine the quality risk in the operations and provides an evaluation of their likely effect. (12) (64) (15)

FMEA is a QRM tool that allows identifying all the potential failures inherent to various parts of the system. Once failures modes are identified it is possible to analyse their effects, their causes and how to avoid them and mitigates their consequences. (64)

When used by the pharmaceutical industry FMEA can be applied to equipment and facilities and might be used to analyse a manufacturing operation and its effect on product or process. It can be applied during the design stage, manufacturing or even in the operations of a system when used in a general context. (12) (64)

The final result obtained with this tool is a list of risk which contains the effects and criticality of failures. The list provides useful information that enables the prioritization of the actions (64).

The strengths of FMEA include the identification of failure modes, their possible causes, and effects, a highlight of the most critical failures, and the detection of problems at an early stage. On the other hand, some inherent limitations are the prolonged and expensive studies, the inability to identify combinations of failure modes and the tedious and complicated analysis/evaluation of the failures (depending on how complex systems are). (64)

##### 2.2.3.2.1 Failure Mode Effects, Critically Analysis (FMECA)

Failure Mode, Effects, and Criticality Analysis is an extension of FMEA. This tool allows a more detailed and critical examination of the failure modes. FMECA is usually a qualitative or semi-quantitative tool. (64)

FMECA indicates the criticality and estimate of the failure mode identified. This tool is usually based on the combination of two parameters, the severity of the

consequences and the likelihood of occurrence. However, a third parameter can be used in the assessment, the difficulty of detection, which assesses the extent of detection of the failure. (15) (64)

This tool provides the same benefits and limitations than FMEA.

#### 2.2.3.3 *Hazard Analysis and Critical Control Points (HACCP)*

The Hazard Analysis and Critical Control Point (HACCP) consist in a tool that provides a structure for identifying hazards and control them at all relevant parts of the process. This tool aims to ensure that risks are minimised by controls throughout the process rather than through inspection of the end product. (64)

HACCP is traditionally considered to be a food safety management tool. In fact, this tool was developed to ensure food quality for the NASA space program and currently is most used by the food chain to control risks, especially those related to microbiological contamination. However, despite its origin, the same principles are also increasingly being applied in other industries such as pharmaceutical and medical devices. (64) (65)

The ICH Q9 guideline defines HACCP tool in a few steps, as follows (12):

- *"Conduct a hazard analysis and identify preventive measures for each step of the process";*
- *"Determine the critical control points";*
- *"Establish critical limits";*
- *"Establish a system to monitor the critical control points";*
- *"Establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control";*
- *"Establish system to verify that the HACCP system is working effectively";*
- *"Establish a record-keeping system."*

The HACCP strengths include a science-based documentation that supports quality control and acceptance limits; acknowledgment of how and where process hazards can be prevented, controlled and minimized; a risk control throughout each step of the process. (64)

Its limitations include the necessity of define critical control points (CCP) and control parameters (CP), determine the risks they represent and understand their significance as inputs to the process. Appropriate controls also need to be established. Another important limitation inherent to HACCP is the possibility to miss gradual changes in control parameters, which are statistically significant. (64)

### 2.2.3.4 *Cause and effect diagram (Ishikawa Diagram)*

Ishikawa diagram or cause and effect analysis is a technique usually used to organize data into a structure. This tool allows to identify possible causes of an event and organize them into categories. Ishikawa Diagram is useful to study the relation and interaction between causes and problems. (64) (63)

The Ishikawa Diagram was created by Kaoru Ishikawa at the beginning of the 1960s. The diagram, also known as fishbone diagram because of the resemblance, has the head represented by the "problem" and the bones, represented by causes and sub-causes grouped by categories. These categories vary depending on the scenario. Ishikawa (1966) proposed, especially for industry, that categories used should be based on 6Ms as shown in table below (66):

*Table 21: 6M categories*

| | |
|---|---|
| **Mother Nature** | Related to the environment.<br>Facility's conditions, location, cleanness, humidity, temperature, and "culture" in which the process operates. |
| **Measurement:** | Related to data and records<br>Information generated from the processor during the process. Data that is used to evaluate and ensure its quality. |
| **Man Power:** | Related to employees and Quality Control Unit or anyone involved in the process. especially related to training and skills. |
| **Machines:** | Any machinery/equipment, computers, tools required accomplishing the work. |
| **Materials:** | Any materials used during the process<br>Especially related to raw materials used to produce the final product. |
| **Methods:** | Related to the process<br>Involves the way that process is conducted and the specific needs for doing it (The presence/absence of policies, procedures, rules, regulations, and laws) |

The Ishikawa Diagram strengths include an applicable expert team work, a structured analysis; consideration of all likely hypotheses; graphical easy to read; identification of areas where further data is needed; Identification of contributory factors responsible for effects. (64)

Limitations inherent to this tool are related to the team, with the results, and with the fishbone structure. The team may not have the sufficient expertise to classify the factors. The results obtained with this tool do not enable to produce recommendations because they are incomplete and need to be part of a more detailed analysis. Fishbone structure does not allow the separation of causal factors into more than one category,

meaning that consideration about interactions between the categories may not be done. (64)

#### 2.2.3.5 *Pareto Chart*

The Pareto chart is a tool used to identify significant causes related to the majority of the problems assigned in a process. Pareto principle served as the base to develop this tool; the principle says that about 20% of the causes are account for 80% of the problems. Hence, most of the reliability problems observed can be explained by a few causes and if this few causes are solved majority part of challenges are solved too. (67)

Vilfredo Pareto was an Italian economist and sociologist who conducted a study in Europe in the early 1900s on wealth and poverty. His findings showed that a significant proportion of problems is caused by a small number of reasons. (67)

The Pareto chart orders the data about their importance, which allows the distinction between frequent and infrequent causes of failures. The chart is made by listing all the elements in decrease order and determining their cumulative frequencies. Pareto chart is most used when data can be arranged into categories, and the rank of each category is important. (15)

The purpose to use this tool is to define the participation and contribution of each cause responsible for the problem. Pareto chart highlights the reasons that most contribute to the problem, characteristics that allow analysing the causes that most need attention. (67)

### 2.2.4 The chosen QRM tools

To conduct the risk assessment proposed in this study, some tools were selected as the Pareto chart, the Ishikawa diagram, the PHA and the FMECA.

As above shown, the Ishikawa diagram is an inductive, basic/informal and simple organization data tool. In this way, this tool was selected with the purpose to organize data according to 6M's categories and to investigate what group most contribute to failures.

The Pareto chart was chosen as a supporting statistical tool with the purpose to analyse the contribution of the microbial contamination problem in the drug products recalls from the USA and the UK markets.

The PHA analysis is an inductive and formal tool that allows identifying hazards and their potential effects but cannot estimate the risk. This tool was chosen with the purpose to initiate the risk analysis, obtain preliminary information and develop a ranking of the hazard using a combination of severity and likelihood of occurrence.

FMECA was the second formal tool used to evaluate the non-conformities. This tool allows to estimate the risk and summarise the most important failure. After the primary analysis and the development of an RRI, FMECA is useful to highlight the failures that need most attention thus need to receive prioritised actions.

# 3 Results

In this chapter, the findings are presented in detail. To facilitate the comprehension, databases consulted are divided into two groups, as follow:

- USA Market: FDA Enforcement Report (16) and FDA Warning Letters (18)
- EU Market: MHRA drug safety update (17) and EMA Eudra GMDP (19)

Each section contains results from a unique database. In this way, the results are presented in the following order:

1. FDA recalls
2. FDA warning letters
3. MHRA recalls
4. EMA warning letter

## 3.1 The United States pharmaceutical market

As FDA policies regulate the USA pharmaceutical market, the present study was based on FDA enforcement reports and FDA warning letters databases. The results are presented in following sections.

### 3.1.1 Non-sterile drug products recall

The research conducted in FDA enforcement reports databases showed that over the period of analysis 2008 to February 2016, 2405 drug products were recalled from the USA market. Of this total, 1722 (71%) recalls were from non-sterile drug products and 683 (29%) sterile drug products. Each recall registered in the FDA enforcement report database contains a brief description of the problem, making possible to identify 27 different causes, as shown in Table 22.

In general, contamination is a frequent cause of recalls, and six sorts were identified, such as microbiological contamination, the presence of the foreign substance, the presence of foreign tablets/capsules, chemical contamination, penicillin cross contamination and cross contamination with other products. Together, all sorts of contamination were responsible for 18% of non-sterile drug products recalls with the microbiological contamination as the most significant cause, present in 5,9% of recalls.

*Table 22: Root causes of FDA recall. Source (16)*

| Causes | Absolute Frequency | Relative Frequency |
|---|---|---|
| *Labelling* | 201 | 11,7% |
| *Marketed without an Approved NDA/ANDA* | 169 | 9,8% |
| *Failed Impurities/Degradation Specifications* | 164 | 9,5% |
| *Failed Dissolution Specifications* | 163 | 9,5% |
| *cGMP Deviations* | 157 | 9,1% |
| *Sub-potent Drug* | 138 | 8,0% |
| ***Microbial Contamination of Non-Sterile Products*** | **101** | **5,9%** |
| *Failed Tablet/Capsule Specifications* | 98 | 5,7% |
| ***Presence of foreign substance*** | **80** | **4,6%** |
| *Defective Delivery System* | 74 | 4,3% |
| *Failed Stability Specifications* | 65 | 3,8% |
| ***Presence of Foreign Tablets/Capsules*** | **59** | **3,4%** |
| *Super-potent Drug* | 54 | 3,1% |
| ***Chemical Contamination*** | **44** | **2,6%** |
| *Mispacked* | 26 | 1,5% |
| *Discoloration* | 19 | 1,1% |
| *Failed Content Uniformity Specifications* | 15 | 0,9% |
| ***Penicillin Cross Contamination*** | **14** | **0,8%** |
| *Incorrect/Undeclared Excipients* | 14 | 0,8% |
| ***Cross Contamination with Other Products*** | **13** | **0,8%** |
| *Misbranded* | 12 | 0,7% |
| *Presence of Precipitate* | 10 | 0,6% |
| *Crystallization* | 10 | 0,6% |
| *Incorrect product formulation* | 7 | 0,4% |

| | | |
|---|---|---|
| *Temperature Abuse* | 6 | 0,3% |
| *Tablets/Capsules Imprinted with Wrong ID* | 5 | 0,3% |
| *Resuspension Problems* | 4 | 0,2% |

#### 3.1.1.1 *Pareto chart*

All the causes responsible for recalls and their frequencies were listed in descending order. Then, the cumulative frequency was calculated with the purpose to build the Pareto chart (Figure 7).

Figure 7 shows that microbiological contamination is the seventh cause that most contributes for recalls of non-sterile drug products in USA market and thus one of the top ten reasons.

The first ten causes have a cumulative frequency of almost 80%, meaning that 80% of the problems are concentrated in only ten reasons, and manufacturers should mainly focus their efforts on these causes to decrease the number of recalls.

Although all causes responsible for recalls are important, those related to the manufacturing process deserve particular attention since they indicate a failure to comply with cGMP.

#### 3.1.1.2 *Microbiological Contamination*

As shown in Table 22, microbiological contamination was responsible for 101 recalls over the period of study. These recalls were thoroughly investigated and analysed, all compiled data being presented in Annex 1.

The microbiologically related recalls, by a period of analysis, are depicted in Figure 8. Data from 2016 were computed until this February and over this period only one microbiologically related recall was recorded. 2011 was the year when FDA recorded the highest number of these sort of recalls, of which the contamination of alcohol and povidone impregnated dressings (“prep pads”) were mainly responsible for this results, with 21 recalls reported (Figure 9).

To organize data, microbiologically related recalls were grouped by categories of products (Table 23). Although some products are not considered medicines, FDA enforcement report also classified them as drug products recall (16). Table 23 shows the absolute frequency of recalls by categories of drug products.

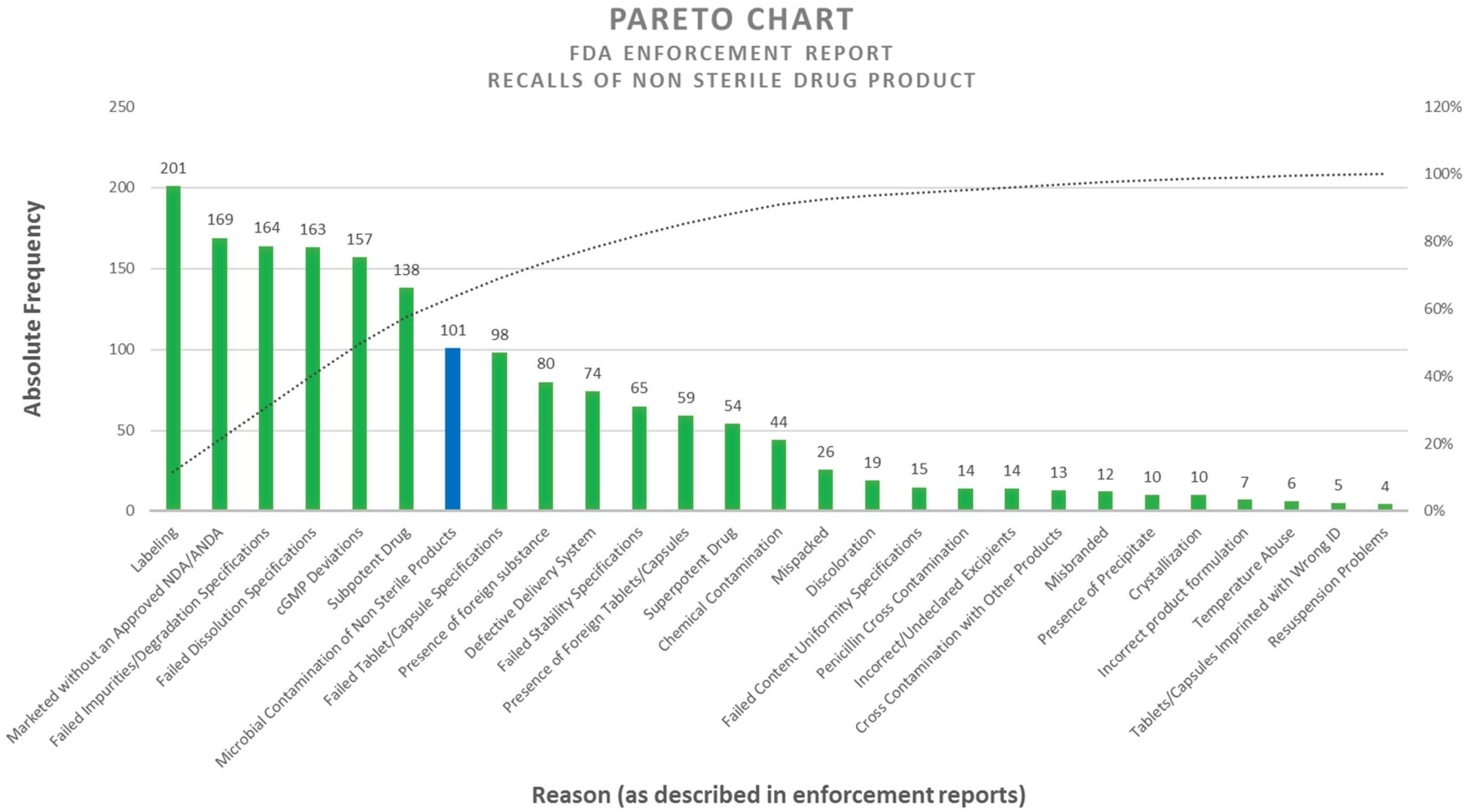



*Figure 7: Pareto Chart - FDA non-sterile drug products recalls*

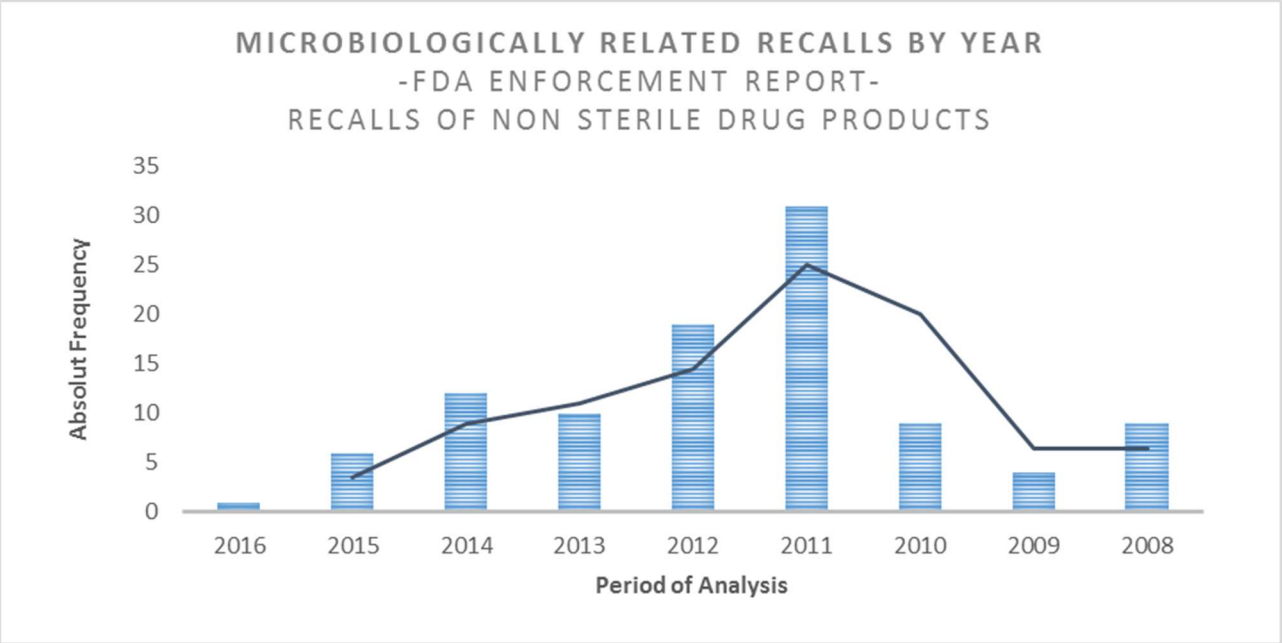
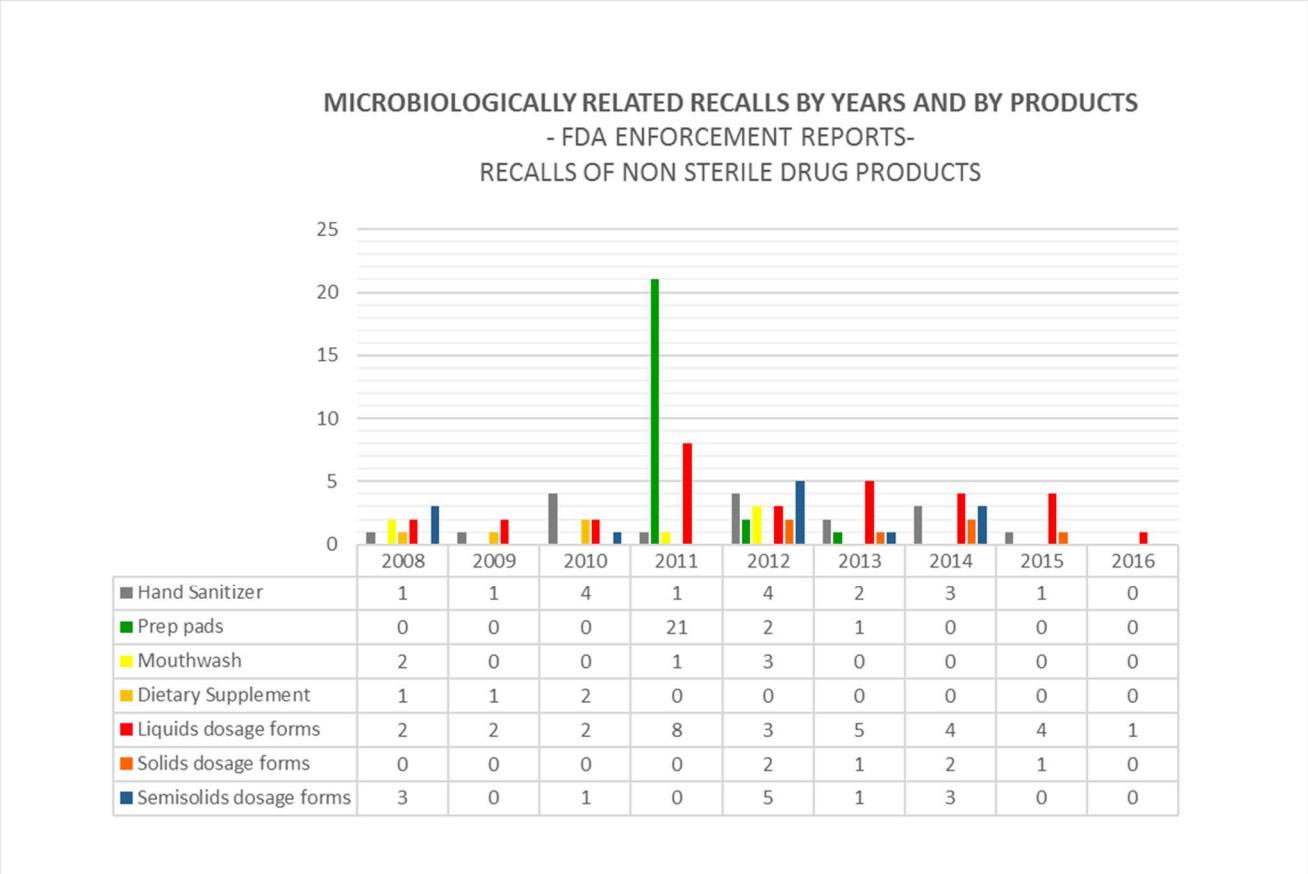



*Figure 8: Microbiologically related recalls by years*




| | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
|---|---|---|---|---|---|---|---|---|---|
| Hand Sanitizer | 1 | 1 | 4 | 1 | 4 | 2 | 3 | 1 | 0 |
| Prep pads | 0 | 0 | 0 | 21 | 2 | 1 | 0 | 0 | 0 |
| Mouthwash | 2 | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 0 |
| Dietary Supplement | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Liquids dosage forms | 2 | 2 | 2 | 8 | 3 | 5 | 4 | 4 | 1 |
| Solids dosage forms | 0 | 0 | 0 | 0 | 2 | 1 | 2 | 1 | 0 |
| Semisolids dosage forms | 3 | 0 | 1 | 0 | 5 | 1 | 3 | 0 | 0 |

*Figure 9: Microbiologically related recalls by years and by-products*

*Table 23: Drug products groups, absolute frequency, and relative frequency of recalls. Source (16)*

| Drug Products | Absolute Frequency | Relative Frequency (%) |
|---|---|---|
| **Liquids dosage forms** | | |
| Topical solution, Topical spray, Oral solution, Oral suspension, Nasal spray, Nasal solution | 31 | 30,7 |
| **Prep pads** | | |
| Alcohol prep pads, Iodine prep pads, Povidone iodine prep pads, Benzalkonium chloride Swabsticks | 24 | 23,7 |
| **Hand Sanitizer** | | |
| Cloths (wipes), Antimicrobial skin sanitizers, Antimicrobial Hand Soap, and Wash Kit | 17 | 16,8 |
| **Semisolids dosage forms** | | |
| Gel, Ointment, Suppository, Lotion, Sunscreen and Cream | 12 | 11,8 |
| **Solids dosage forms** | | |
| Capsules and Tablets | 7 | 6,9 |
| **Mouthwash** | 6 | 5,9 |
| **Dietary Supplement** | 4 | 3,9 |

#### 3.1.1.2.1 Most frequent Microorganism

Although most recalls do not specify the contaminant, 29 of them mentioned *Burkholderia cepacia* as responsible for recalls, 10 mentioned fungi (yeasts and molds) and 9 *Bacillus cereus*. Together these 3 microorganisms were responsible for almost 50% of microbiologically related recalls as shown in Table 24.

*Table 24: Identity of microorganism cited in FDA recalls. Source (16)*

| Microorganism | Number of cited recalls |
|---|---|
| Not Specified | 36 |
| *Burkholderia sp.* | 29 |
| Yeasts/Molds | 10 |
| *B. cereus* | 9 |
| *Pseudomonas sp.* | 4 |
| *E. coli* | 3 |
| *Elizabethkingia meningoseptica* | 3 |
| *Serratia sp.* | 2 |
| *C. difficile* | 2 |
| *Enterobacter gergoviae* | 1 |
| *Achromobacter xylosoxidans* | 1 |
| *Sarcina Lutea* | 1 |
| *Sphingomonas paucimobilis* | 1 |
| *Staphylococcus warneri* | 1 |
| *Stenotrophomas maltophilia* | 1 |

In addition, *B. cepacia*, the most commonly identified microorganism in the recalls of non-sterile drug products, are specially related to liquid dosage forms, hand sanitizers, and mouthwash formulations (Figure 10).

Fungal contamination was cited in 9 recalls, with 5 of these related to liquid dosage forms and 4 with semisolid dosage forms.

*B. cereus* was the most common contaminant microorganisms identified in prep pads, cited in 9 of 24 recalls of these products. It should be noticed that some products were contaminated with more than one species of microorganism. All microorganisms mentioned are presented inTable 24 and Figure 10.

#### 3.1.1.3 *Cause of microbiological contamination*

Despite the fact that recalls contain a brief description of the problem, it was not possible to identify all root causes responsible for microbiologically related recalls. In

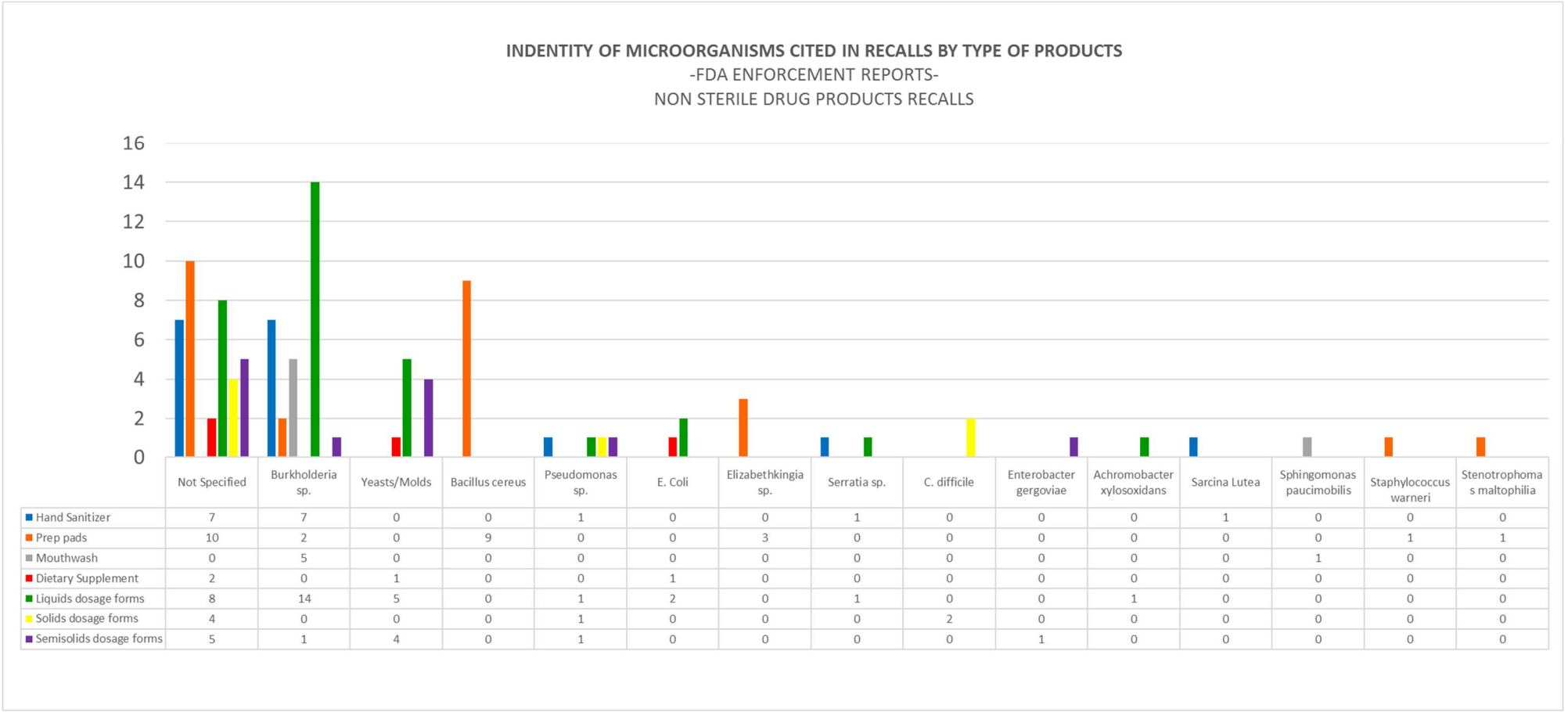
fact, some recall present incomplete information and lack of necessary details. Nevertheless, some causes were identified and summarised in Table 25.

Raw materials were the most frequent source of contamination identified in recalls, responsible for 19 recalls over the period of analysis affecting prep pads, liquid dosage forms, and solid dosage forms as shown in Figure 11. Solid dosage forms were the most affected ones, with 4 out of 7 recalls related to this cause.

Failure in preservative effectiveness was the second most relevant source of contamination. It was responsible for eight recalls over the period of analysis. This failure affected almost all types of products and the products that recorded the largest number was liquid and solid dosage forms (Figure 11).

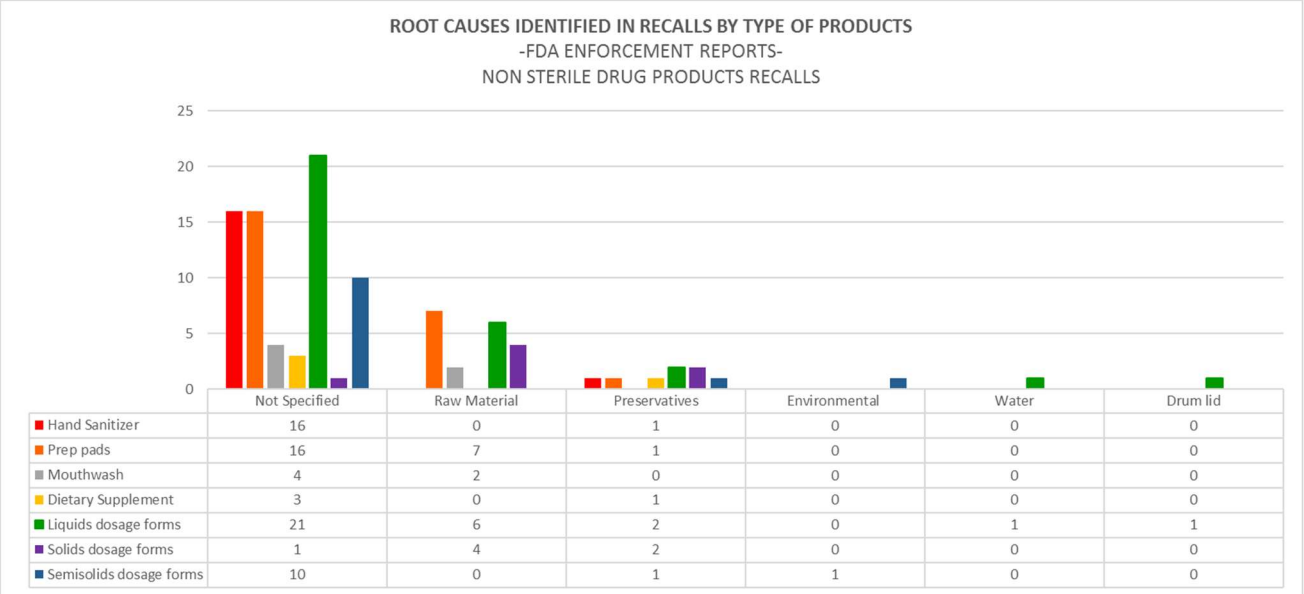
*Table 25: Root causes identified in microbiologically related recall. Source (16)*

| Causes | Absolute Frequency | Relative Frequency |
|---|---|---|
| Not Specified | 71 | 70% |
| Raw material used was contaminated | 19 | 19% |
| Products failed the AET per USP <51> for preservative effectiveness | 8 | 8% |
| Elevated counts of gram-positive rods were found during environmental testing | 1 | 1% |
| Out of Specification (OOS) result for purified water used to rinse product contact parts during manufacturing | 1 | 1% |
| Mold found in gasket area of drum lid | 1 | 1% |




| | Not Specified | Burkholderia sp. | Yeasts/Molds | Bacillus cereus | Pseudomonas sp. | E. Coli | Elizabethkingia sp. | Serratia sp. | C. difficile | Enterobacter gergoviae | Achromobacter xylosoxidans | Sarcina Lutea | Sphingomonas paucimobilis | Staphylococcus warneri | Stenotrophomas maltophilia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hand Sanitizer | 7 | 7 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Prep pads | 10 | 2 | 0 | 9 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Mouthwash | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Dietary Supplement | 2 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Liquids dosage forms | 8 | 14 | 5 | 0 | 1 | 2 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Solids dosage forms | 4 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Semisolids dosage forms | 5 | 1 | 4 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |

*Figure 10: Identity of microorganisms cited in recalls by type of product.*




| | Not Specified | Raw Material | Preservatives | Environmental | Water | Drum lid |
|---|---|---|---|---|---|---|
| Hand Sanitizer | 16 | 0 | 1 | 0 | 0 | 0 |
| Prep pads | 16 | 7 | 1 | 0 | 0 | 0 |
| Mouthwash | 4 | 2 | 0 | 0 | 0 | 0 |
| Dietary Supplement | 3 | 0 | 1 | 0 | 0 | 0 |
| Liquids dosage forms | 21 | 6 | 2 | 0 | 1 | 1 |
| Solids dosage forms | 1 | 4 | 2 | 0 | 0 | 0 |
| Semisolids dosage forms | 10 | 0 | 1 | 1 | 0 | 0 |

*Figure 11: Root causes identified in recalls by type of product*

### 3.1.2 Warning Letters

Over the period of analysis 2008 to February 2016, FDA issued 143 WLs. Of this total, 97 WLs were addressed to companies that manufacture non-sterile products as API (52 WLs) and finished products (45 WLs). This study aims at analysing only the latter.The complete information is available in Annex 2.

The analysis conducted with the WLs addressed to the manufacturer of non-sterile finished products, identified 52 types of violations in cGMP. Each violation or non-conformity had their likelihood of occurrence defined by the number of citations in WLs. The most cited ones are present in Table 26.

*Table 26: FDA - Non-Conformities and their occurrence in warning letters. Source (18)*

| Non-Conformities | Occurrence |
|---|---|
| *Your firm has not established written production and control procedures to assure that the drug products produced have the identity, strength, quality and purity they purport or are represented to possess.* | 18 |
| *Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed.* | 15 |
| *The written stability testing program is inadequate to assess the stability characteristics of drug products and for determining appropriate storage conditions and expiration dates.* | 13 |

#### 3.1.2.1 *Ishikawa Diagram*

The Ishikawa diagram was constructed using all of the 52 NC identified without any screening process. Each NC was classified using the perception of the author, the complete classification is available in Annex 2 and the Ishikawa diagram illustrated in Figure 12.

The effect being investigated was microbiological contamination in pharmaceutical industries and the causes used to build the “bones of the fish” were the NC collected from FDA WLs. The categories adopted to group the causes were the 6M’s as proposed by Kaouru Ishikawa (1972) and described in section 2.2.3.4 above. Table 27 shows these categories and the percentage of NC grouped in each one of them.

Most of the non-conformities were grouped into Method category, which has 33% of NC as illustrated in Figure 12. These results show that major part of the causes are related to how the process is performed and the specific requirements for doing so, such as policies, procedures, methodologies, rules, regulations and laws. The second most expressive category was Man Power with 27% of NC, indicating a considered number of causes are related to the employees involved in the process (Figure 12).

*Table 27: FDA - 6M's categories and their percentage*

| Categories | Percentage |
|---|---|
| Materials | 12% |
| Mother Nature | 1% |
| Machinery | 12% |
| Man Power | 27% |
| Measurements | 15% |
| Methods | 33% |

### 3.1.2.2 *Preliminary Hazard Analysis (PHA) – FDA*

The PHA analysis was conducted with the cooperation of Portuguese ISO committee. All NC were analysed regarding severity and likelihood of occurrence in the local industries.

The RRI was obtained using the combination of severity and likelihood of occurrence. For comparison purposes, two different RRI were developed: one using the likelihood defined by the ISO committee's expertise and the other one using the likelihood found in WLs issued by FDA. The complete RRI are available in Annex 2.

Table 28 and Table 29 shows the NC that received the highest scores on the indices. Crucial differences were observed among RRI. The index obtained with ISO committee's expertise, shows that 49% of risks are low, and 51% are moderate, while no risks were classified as High. This suggests that major risks are related to raw material quality assurance and with process controls validation. The second NC presented in Table 28 also received a high score. However, as in a general understanding, this failure does not relate to microbiological contamination, it was not taken into consideration.

The RRI obtained with the likelihood of occurrence found in WLs issued by FDA showed that 52% of risk are low, 40% are moderate, and 8% are high. These results point out that major risks are related to the research and investigation policies adopted by companies, with the stability testing program, and with the control procedures.

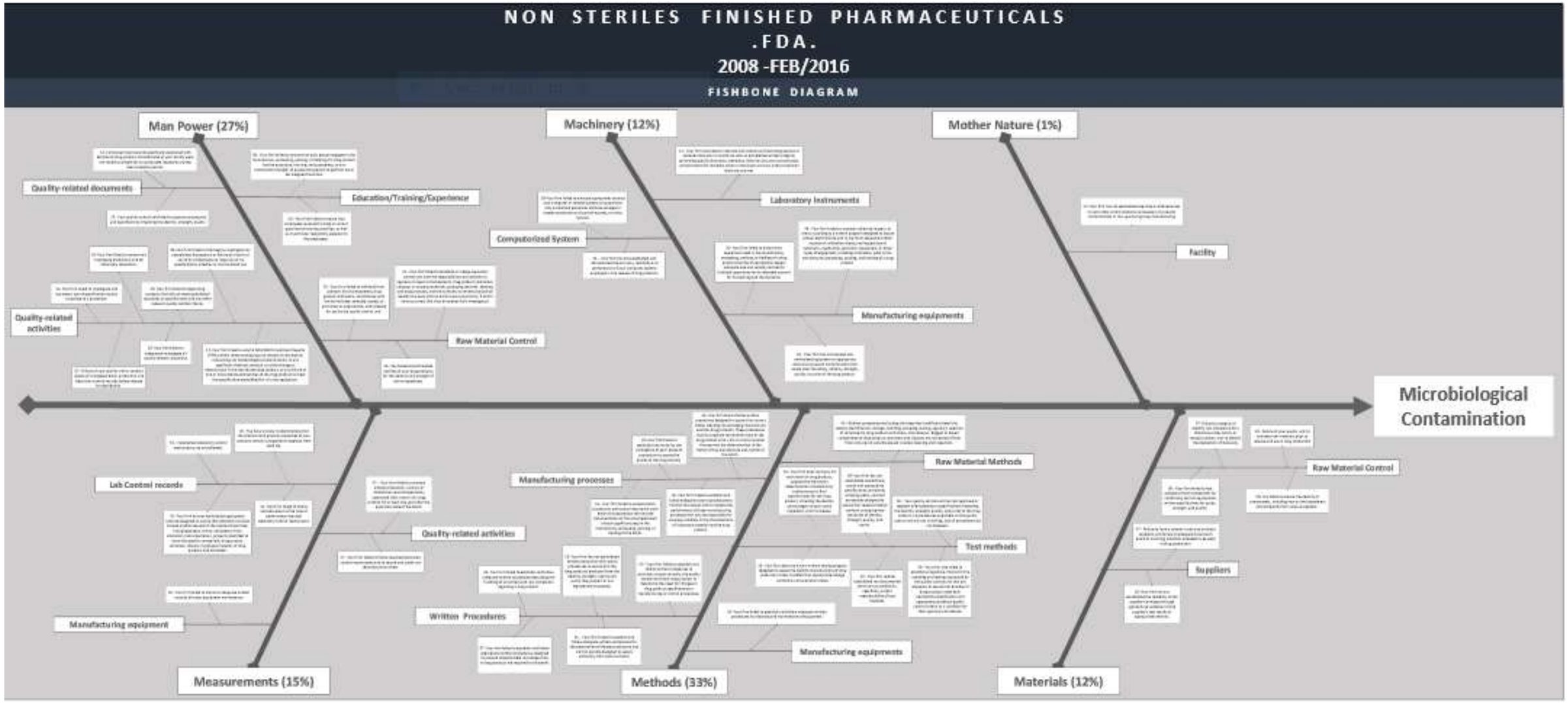



*Figure 12: FDA - Ishikawa Diagram*

*Table 28: Highest scores obtained in Risk-Ranking Index using the likelihood of occurrence defined by ISO committee's expertise. Source (18)*

| Non-Conformities | Score | Risk Classification |
|---|---|---|
| *Your firm has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.* | 9 | Moderate |
| *Your firm failed to establish time limits for the completion of each phase of production and to assure the quality of the drug product.* | 9 | Moderate |
| *Your firm failed to establish and follow adequate control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.* | 9 | Moderate |

*Table 29: Highest scores obtained in Risk-Ranking Index using the likelihood found in WLs issued by FDA. Source (18)*

| Non-Conformities | Score | Risk Classification |
|---|---|---|
| *Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed.* | 25 | High |
| *The written stability testing program is inadequate to assess the stability characteristics of drug products and for determining appropriate storage conditions and expiration dates.* | 25 | High |
| *Your firm has not established written production and control procedures to assure that the drug products produced have the identity, strength, quality and purity they purport or are represented to possess.* | 25 | High |

### 3.1.2.3 *Failure Mode Effects, Critically Analysis - FMECA*

The introduction of a 3rd parameter in the analysis of non-conformities allowed developing a risk estimation and an RPR. Like the other two parameters the "difficulty of detection" was also classified with ISO group cooperation.

A “low, moderate, and high” rating scale was used to evaluate "Severity, likelihood of occurrence, and difficulty of detection". This rating scale produces 18 possible results with 5 of them considered first prioritization as illustrated in Table 7 presented in section 1.3.2.4.

The RPR scale obtained with FMECA analysis showed that almost all of non-conformities identified by FDA were classified as a 3rd priority failure (1-9 scores), and only one non-conformity was classified as a 2nd priority failure (15-27 scores). Table 30 shows the NCs that received the highest scores and were ranked as a 3rd and 2nd priority (9 and 27 scores). The complete RPR developed with FDA WLs is available in Annex 3.

*Table 30: FDA- Highest scores obtained in Risk-Priority Rank using the likelihood of occurrence defined by ISO group. Source (18)*

| Non-Conformities | Score | Risk Priority |
|---|---|---|
| *Your firm failed to establish and follow adequate control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.* | 27 | 2nd priority |
| *Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions.* | 9 | 3rd priority |
| *Your firm failed to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data..* | 9 | 3rd priority |
| *Your firm has not established the reliability of the supplier’s analyses through appropriate validation of the supplier’s test results at appropriate intervals.* | 9 | 3rd priority |
| *Your firm failed to establish time limits for the completion of each phase of production to assure the quality of the drug product.* | 9 | 3rd priority |
| *Your firm failed to establish and follow written procedures to evaluate, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.* | 9 | 3rd priority |

For comparison purposes, a second RPR was also developed for FMECA analysis. The rank obtained with the likelihood of occurrence found in WLs issued by FDA showed that 90% of NCs were classified as a 3rd priority and the remaining 10% as a 2nd priority. Table 31 shows the NCs that received the highest scores and, in this case, classified as 2nd priority. (25-27 scores)

*Table 31: Highest scores obtained in Risk-Priority Rank using the likelihood of occurrence found in WLs issued by FDA. Source (18)*

| Non-Conformities | Score | Risk Priority |
|---|---|---|
| *Your firm failed to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data.* | 27 | 2nd priority |
| *Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed.* | 25 | 2nd priority |
| *Your firm has not established written production and control procedures to assure that the drug products produced have the identity, strength, quality and purity they purport or are represented to possess.* | 25 | 2nd priority |
| *The written stability testing program is inadequate to assess the stability characteristics of drug products and for determining appropriate storage conditions and expiration dates.* | 25 | 2nd priority |

As the results show, the introduction of a third parameter "difficulty of detection" reinforce the results obtained with PHA. The most critical failures are the ones that received highest scores.

## 3.2 European Pharmaceutical Market

As EMA policies regulate the EU pharmaceutical market, the present study was based on the EMA EudraGDMP database, where WLs were collected (19). Regarding recalls, the databases consulted were those from the MHRA drug safety update, which only reflect the UK pharmaceutical market (17). The results are presented in following sections.

### 3.2.1 MHRA Recalls

According to MHRA databases, 94 drug products were recalled from UK market over the years 2008 to Feb 2016. Of this total, 47 (50%) recalls were from non-sterile drug products and 47 (50%) of sterile drug products.

The MHRA databases also present a brief description of the problems that led to drug product recalls, allowing to identify 17 different causes (Table 32).

Contamination is also a frequent cause for recalls in UK market. In total, four sorts were identified, such as microbiological contamination, the presence of the foreign substance, the presence of foreign tablets/capsules and chemical contamination. Together, they accounted for almost 30% of non-sterile drug product recalls. Microbiological contamination was present in 6,4% of recalls.

*Table 32: Root causes for MHRA recalls. Source (17)*

| Causes | Absolute Frequency | Relative Frequency |
|---|---|---|
| *Labelling* | 7 | 14,9% |
| ***Presence of foreign substance*** | **7** | **14,9%** |
| *leaflet information* | 5 | 10,6% |
| *Benefits no longer outweigh the risks* | 5 | 10,6% |
| *Failed impurities/degradation specifications* | 3 | 6,4% |
| ***Presence of Foreign Tablets/Capsule*** | **3** | **6,4%** |
| ***Microbial Contamination of non-sterile Products*** | **3** | **6,4%** |
| *Not manufactured in line with GMP requirements* | 3 | 6,4% |
| *No longer meet the requirements for supply* | 2 | 4,3% |
| *Failed stability specifications* | 2 | 4,3% |
| *Failed Tablet/Capsules specification* | 1 | 2,1% |
| *Supply chain not adequate* | 1 | 2,1% |
| *Defective delivery system* | 1 | 2,1% |
| ***Chemical Contamination*** | **1** | **2,1%** |
| *Super potent drug* | 1 | 2,1% |

| | | |
|---|---|---|
| *Mispacked* | 1 | 2,1% |
| *Failed specification for child resistance* | 1 | 2,1% |

#### 3.2.1.1 *Pareto Chart*

Figure 13 shows that microbiological contamination is one of the top ten causes responsible for recalls in UK pharmaceutical market. It has the same relevance than others causes, such as "*Failed impurities/degradation specifications*", "*Presence of foreign Tablets/Capsule*" and "*Product not manufactured in line with GMP requirements*".

The first ten causes have a cumulative frequency of almost 85%. This means that 85% of the problems, in UK pharmaceutical market, are concentrated in only ten reasons.

#### 3.2.1.2 *Microbiological Contamination*

Although in a much smaller proportion of data volume, recalls recorded by MHRA showed similar results than recalls recorded by FDA (Table 33). Raw material contamination and failure in preservative effectiveness were also cited as causes that led to drug products recalls. Fungal and bacterial contamination were also identified in related recalls, although the bacterium concerned was *Enterococcus faecium* rather than *B. cepacia*.

*Table 33: The UK microbiologically related recalls. Source (55)*

| Year | Pharmaceutical Dosage Form | Products | Microorganisms | Cause |
|---|---|---|---|---|
| 2015 | Solid dosage form | Capsules | Fungi | Not Specified |
| 2013 | Liquid dosage form | Oral Suspension | *Enterococcus faecium* | Raw material contamination |
| 2013 | Semisolid dosage form | Gel | Not Specified | Failure in preservative effectiveness |

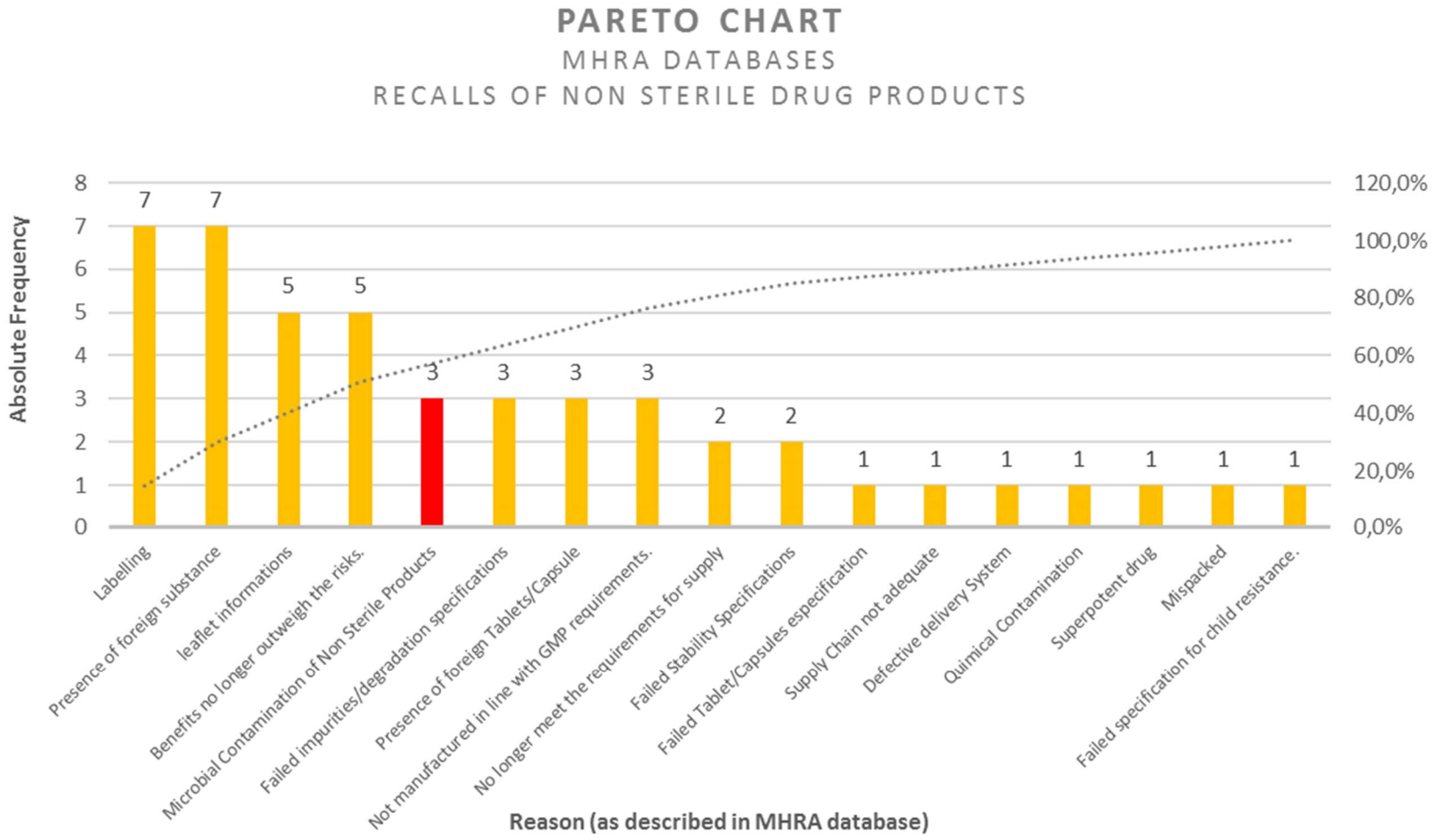



*Figure 13: Pareto chart - MHRA non-sterile drugs recalls*

### 3.2.2 EMA Warning Letters

According to the EMA EudraGMDP databases, over the period of analysis, EMA issued 112 WLs, 93 of which (83%) were addressed to companies that manufacture non-sterile products as API (65 WLs) and finished products (28 WLs). All compiled data are available in Annex 4.

The analysis conducted with the WLs issued to manufacturers of non-sterile finished products identified 63 NC in EU cGMP. Each NC had its likelihood of occurrence defined by the number of citations in the WLs. The most cited ones are present in Table 34.

*Table 34: EMA - Non-conformities and their occurrence in Warning Letters. Source (19)*

| Non-Conformities | Occurrence |
|---|---|
| *Record integrity and veracity: some records were made up or altered.* | 11 |
| *There was a continued failure of the Quality Management System and Quality Assurance to establish compliance with EU GMP.* | 10 |
| *Lack of appropriate root causes investigation into deviations.* | 8 |

#### 3.2.2.1 *Ishikawa Diagram*

The Ishikawa diagram created using all of the 63 NCs identified in EMA WLs without any screening process. Each NC was classified using the perception of the author. Table 35 shows the results obtained and the percentage of NC grouped in each one of the 6M categories. A complete classification is available in Annex 4, and the Ishikawa Diagram is illustrated in Figure 14.

*Table 35: EMA - 6M's categories and their percentage*

| Categories | Percentage |
|---|---|
| Materials | 10% |
| Mother Nature | 11% |
| Machinery | 13% |
| Man Power | 27% |
| Measurements | 14% |
| Methods | 25% |

Most of the NCs were grouped into Man Power's category, which accounted for 27% of NC as shown in Table 35. These results show that most of the causes are related to employees involved in the process. Methods were the second group that receives the most percentage of NC 25%; that means that a high number of failures identified by Inspectors are related to the process and its specific needs. EMA results are very similar to FDA results. However, NC identified by EMA authorities are more widely distributed into 6M categories.

#### 3.2.2.2 *Preliminary Hazard Analysis (PHA) - EMA*

NCs identified by EMA authorities were also analysed with ISO group cooperation. The group defined severity and likelihood of occurrence using a "low, moderate and high" rating scale. The complete results are available in Annex 4.

The RRI was obtained using the combination of severity and likelihood of occurrence. The parameter likelihood of occurrence used in the analysis was defined by ISO group expertise and by the occurrence found in WLs. Table 36 shows the NC that received the highest scores on indices.

The RRI obtained with ISO committee's expertise, indicates that 18% of risks are low, 76% are moderate, and 6% are High. This suggests that significant risks are related to lack of investigations, cleaning procedures, complaints and quality agreements as shown in Table 36.

The RRI obtained with the likelihood of occurrence found in WLs issued by EMA revealed that 21% of risk are low, 74% are moderate, and 5% are high. These results point out that significant risks are related to the research and investigation of results out of specification (OOS) policies adopted by companies and integrity and veracity of data (Table 37).

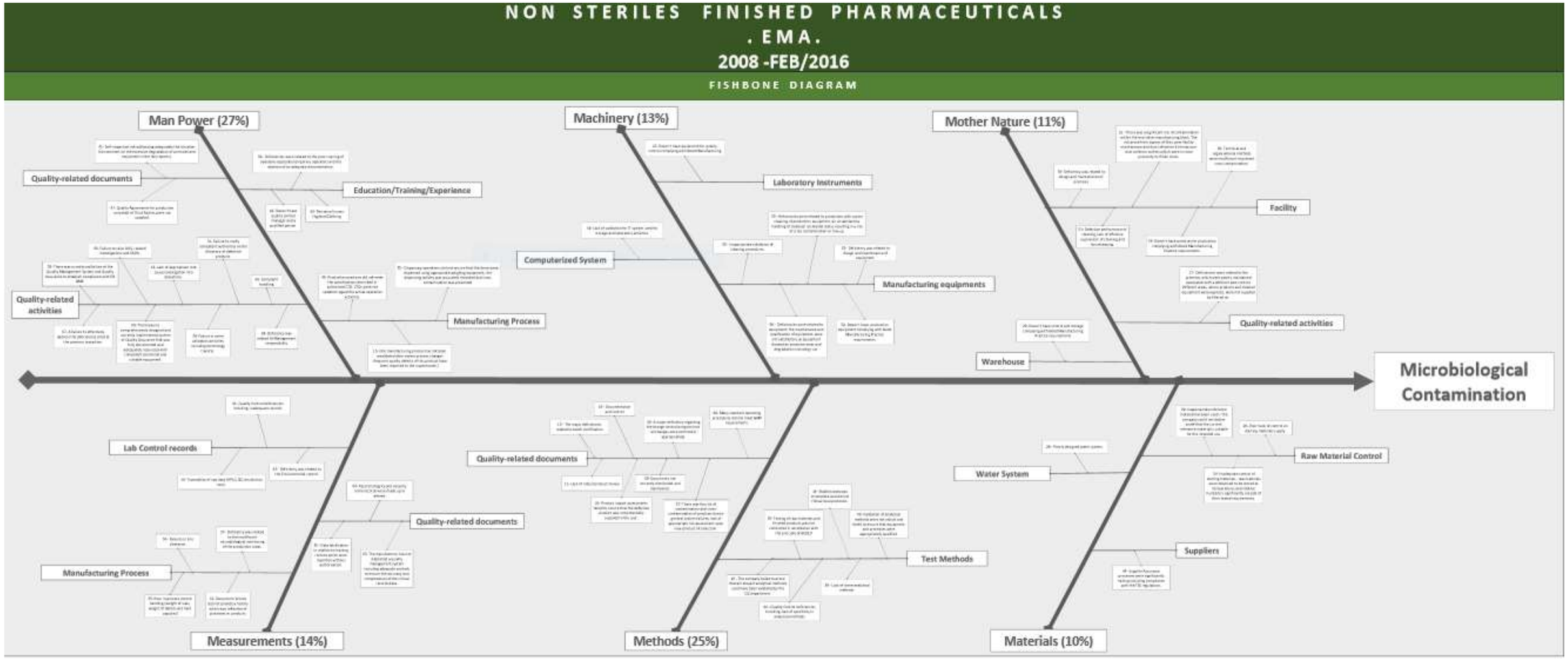



*Figure 14: EMA - Ishikawa Diagram*

*Table 36: EMA - Highest scores obtained in Risk-Ranking Index using the likelihood of occurrence defined by ISO committee's expertise. Source (19)*

| Non-Conformities | Score | Risk Classification |
|---|---|---|
| *Failure to raise OOS, related investigations and CAPA.* | 15 | High |
| *Inappropriate validation of cleaning procedures.* | 15 | High |
| *The deficiency was related to Complaint handling.* | 15 | High |
| *Quality Agreements for production on behalf of Third Parties were not updated.* | 15 | High |

*Table 37: EMA - Highest scores obtained in Risk-Ranking Index using the likelihood of occurrence found in WLs issued by EMA. Source (19)*

| Non-Conformities | Score | Risk Classification |
|---|---|---|
| *There was a continued failure of the Quality Management System and Quality Assurance to establish compliance with EU GMP.* | 25 | High |
| *Record integrity and veracity: some records were made up or altered.* | 25 | High |
| *Failure to raise OOS, related investigations and CAPA.* | 15 | High |

#### 3.2.2.3 *Failure Mode Effect, Critically Analysis (FMECA) – EMA*

The RPR obtained with FMECA and using the likelihood of occurrence defined by ISO group showed that 51 of NCs were classified as a 3rd priority, 11 as 2nd and only 1 were classified as 1st priority. Table 38 shows the non-conformities that received the highest scores and were ranked as a 1st and 2nd priority (27 and 45 scores).

The RPR obtained with the likelihood of occurrence found in WLs issued by EMA showed that 53 of NC were classified as a 3rd priority, 9 as a 2nd priority and 1 as a 1st priority. Table 39 shows the NC that received the highest scores and was classified as a 1st and 2nd priority (25-75 scores). The complete results are available in Annex 5.

*Table 38: EMA - Highest scores obtained in Risk-Priority Rank using the likelihood of occurrence defined by ISO group. Source (19)*

| Non-Conformities | Score | Risk Priority |
|---|---|---|
| *Quality Agreements for production on behalf of Third Parties were not updated.* | 45 | 1st Priority |
| *Deficiencies were related to the poor training of operators especially temporary operators and the absence of adequate documentation.* | 27 | 2nd Priority |
| *Lack of appropriate root causes investigation into deviations.* | 27 | 2nd Priority |

*Table 39: EMA - Highest scores obtained in Risk-Priority Rank using the likelihood of occurrence found in WLs issued by EMA. Source (19)*

| Non-Conformities | Score | Risk Priority |
|---|---|---|
| Record integrity and veracity: some records were made up or altered. | 75 | 1st Priority |
| Lack of appropriate root causes investigation into deviations. | 27 | 2nd Priority |
| There was a continued failure of the Quality Management System and Quality Assurance to establish compliance with EU GMP. | 25 | 2nd Priority |

# 4 Discussion

## 4.1 Results obtained

Relevant information was achieved with the documentary analysis. Recalls provide a statistical view about microbiological contamination while WLs provide give information about failures and hazards observed in the manufacturing process. Some findings must be discussed in detail, such as the high number of citations involving *B. cepacia* in recalls of non-sterile drug products in USA market, a significant number of citations involving fungal contamination, raw material contamination, failure in preservatives effectiveness and the most frequent failures committed by manufacturers. The following sections will cover these issues.

### *4.1.1 Burkholderia sp.*

The presence of bacteria from genus *Burkholderia* in drug products is not new information. As mentioned above, the findings obtained by Scott Sutton (2012) showed this microorganism was cited 34 times in recalls of non-sterile drugs, devices and healthcare products registered over the period of 2004-2011 (6). This work identified 29 citations only in drug products with 13 of them recorded after 2011. These results show that bacteria from genus *Burkholderia*, especially *B. cepacia* are still a cause for serious concern.

As reported by Lynn Torbeck, et al. (2011), the genus *Burkholderia* currently comprises more than 60 species. Further analysis divided the *B. cepacia* into 17 closely related species called *Burkholderia cepacia* complex (Bcc) (7). These species are common in nature and can be found almost everywhere. As regard to patients' safety, infections caused by Bcc have occurred worldwide, posing highest risks to the immunocompromised populations. The worst consequences known are related to patients with deficiencies in immune systems or chronic lung disease, especially CF. Pneumonia and bacterial infections are the most dangerous conditions observed. (7). There is evidence that contamination with Bcc is related to drug products, cosmetics, disinfectants, and preservatives (7). Apparently, the contamination of the latter may be due to the use of preservatives in these aqueous dosage forms, particularly ammonium quaternary compounds, which may select Bcc (68).

Besides being widely distributed in nature, Bcc is organism's resistant to many disinfectant cleansers and is unaffected by many preservatives. The detection and removal of Bcc is a challenge for pharmaceutics. In fact, the microbiological test methods devoted to non-sterile drug products provided by USP or EP may produce false negative results. Although commonly found in drug products and responsible for severe

conditions, Bcc is not present on a panel of challenge microorganism in EP and USP tests. Therefore, the presence/absence test is not able to evaluate it. (7) (22)

The present study identified Bcc as the most common contaminant of aqueous liquid products, being cited in 14 recalls of liquid dosage forms, 7 in hand sanitizers and 5 in mouthwash formulations. In fact, water is the main source of contamination and a potential reservoir of *B. cepacia*. (7) (68)

To avoid contamination with Bcc, pharmaceutical companies have the responsibility to monitor and establish controls, especially related to water. Any source of water must be considered a potential reservoir of Bcc, as well as any process that involves water, such as cleaning, disinfecting, and drying of equipment. (7)

The analysis of WLs showed that failures related to process controls are common among industries that received FDA WLs (Table 40).

*Table 40: FDA - Non-conformities related to process control. Source (18)*

| **FDA: Non-Conformities related to process control** |
|---|
| *Your firm failed to establish and follow appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile.* |
| *Your firm has not established written production and control procedures to assure that the drug products produced have the identity, strength, quality and purity they purport or are represented to possess.* |
| *Your firm failed to establish and follow adequate control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.* |

Failures related to cleaning, disinfecting and drying were also registered by FDA inspectors (Table 41).

*Table 41: FDA - Non-conformities related to cleaning process. Source (18)*

| **FDA: Non-Conformities related to cleaning process** |
|---|
| *Your firm failed to ensure that equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size and suitably located to facilitate operations for its intended use and its cleaning and maintenance.* |
| *Your firm has not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product.* |
| *Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment.* |

These results showed that those manufacturers do not have strict daily operational control, and thus these failures may facilitate the contamination and proliferation of bacteria, especially from genus *Burkholderia.*

### 4.1.2 Fungal Contamination

Fungal contamination was also a frequent cause responsible for recalls. In the USA market, the prevalence of recalls that specifically cited fungal contamination was 9%, whereas the UK this sort of contamination was mentioned in one of three microbiologically related recalls.

In literature, it is possible to find significant cases of outbreaks diseases associated with fungal contamination (8). Table 42 shows cases of fungal contamination in drug products and the main species of eukaryotic microorganisms responsible.

*Table 42: Mold associated with infection outbreaks and drug recalls: multiple countries 2009–2013. Source (8)*

| Main Species Complex | Product | Patients | Disease |
|---|---|---|---|
| *Rhizopus microsporus* | Allopurinol tablets | 12 | Intestinal zygomycosis |
| *Fusarium solani* | Cefuroxime basic salt solution | 9 | Endophthalmitis |
| *F. incarnatum– equiseti* | Brilliant Blue Green dye | 21 | Endophthalmitis |
| *Bipolaris hawaiiensis* | Triamcinolone | ~26 | |
| *Exserohilum rostratum* | Methylprednisolone acetate | ~100 | Meningitis |
| *Aspergillus fumigatus* | | 1 | Meningitis |
| Mixed species? (*Paecilomyces formosus*) | | ~650 | Spinal epidural Abscesses - meningitis |
| *Aspergillus (Alternaria, Cladosporium Penicillium)* | Methylprednisolone acetate | 1,~26? | Skin abscesses |

The severity of the fungal contamination and extent of the hazards depends on the drug products, route of administration and the in particular patient's resistance (8). According to Tim Sandle (2014), contaminated air and skin are the two principal causes of hazards to patients. Drug products intended for the nasal route of administration can carry airborne fungal spores that may be harmful to patients. Likewise, topical formulations, like creams and ointments, can transport spores through the rubbing of the skin (1).

In this context, the main risk factors reported by Tim Sandle (2014) are poorly ventilated areas or clean rooms with insufficient air changes, areas subjected to large amounts of humidity and where there are ridges or cracks in finishes (1). Furthermore, some factors may influence and affect the likelihood of fungi surviving such as changes to environmental conditions (e.g. a rise in ambient temperature; air humidity); personnel behaviour and hygiene; biocide efficacy; ineffective cleaning; the time of year; and the geographical environment (1).

In addition to the usual risks related to the manufacturing process, the conditions of storage and transportation as well as the in-use, when repeated withdrawal of individual doses from a multi-dose container, may represent a risk to the microbial product quality. This risk should be minimised by establishing a period of which a multidose product can be used while retaining quality within an accepted specification once the container is opened (70).

Although this risk may be minimized with the addition of an effective, antimicrobial preservative (32), it should be unequivocally stated that they cannot be used as an alternative to GMP (31).

In this way, fungal contamination may also be an indication that antimicrobial preservative has failed. In fact, the AET prescribed by the USP and the EP does not allow the increase of mold or yeast from the initial level of inoculation in a test sample containing preservatives. (34) (35)

Another problem with fungus contamination is the visual impact because the presence of mold and yeast in drug products discourage the patient from taking the medication and may damage the company's reputation more than other type contamination.

The analysis of WLs showed that failures related to the environment (facilities) are common among industries that received WLs, poor maintenance, deficiencies in pest control, poor design and lack of air filtration were NC commonly pointed by EMA.

*Table 43: FDA - Non-conformities related to the environment. Source (19)*

| **EMA: Non-Conformities related to environment** |
|---|
| *Deficiencies were related to the premises which were poorly maintained associated with a deficient pest control. Different areas, where products and cleaned equipment were exposed, were not supplied by filtered air.* |
| *The deficiency was related to the insufficient microbiological monitoring of the production areas.* |
| *The deficiency was related to the environmental control.* |
| *The deficiency was related to design and maintenance of premises.* |

### 4.1.3 Failure in Antimicrobial Effectiveness Test

Failure in the AET was directly responsible for 8 recalls of non-sterile drug products in the USA market and 1 in the UK market. Taking into consideration that this test is not a batch release, these numbers might be greater than previously thought since microbial contamination may be indicative of the failure in preservative effectiveness. (33)

The selection of preservatives should be based on several criteria such as the site of use (internal or external), the spectrum of microorganism that it is active, its shelf life, toxicology, compatibility with the ingredients and relatively free of taste and odor. (71) (31)

Many reasons can be associated with preservatives failure, including the most widely studied interactions of ingredients, excipients, and containers. Preservatives possess reactive functional groups and have singularities that need to be considered when formulating the drug product (72). A good example is the use of macromolecules such as cellulose derivatives, polyethylene glycol, and tragacanth gum that depending on the preservative used in the formulation may cause its failure due to binding and adsorption. (71)

Other factors may compromise preservative effectiveness, as chemical instability and physical losses or changes. To mitigate these risks industries must truly know all of the components used in the formulation and conduct appropriate pre-formulation studies to determine interaction and possibilities for degradation (72). Indeed, compatibility of excipients with the drug substance and with other excipients should be established during pharmaceutical development, also demonstrating their ability remain active throughout the drug product shelf life (73).

The AET is required to evaluate the efficacy of preservatives added to the formulations. This test is often performed during drug development and is not considered a batch release test (33). However, ICH Q6A suggest that this test should usually be carried out at release or under certain circumstances during the manufacturing. (74) (25).

According to Sutton (2010), it is prudent that the GMP-mandatory post-approval market stability programs in place include the preservative effectiveness throughout shelf-life. An annual time point assay can provide useful information. (33)

The documentary analysis using reports of WLs showed that Stability Tests Programs (STP) are inadequate in a considerable number of industries that receive WLs from FDA. Failure to assess the stability characteristics of drug products and determining appropriate storage conditions and expiration dates were cited in 7% of WLs analysed (Table 44).

*Table 44: Non-conformities related to Stability Test Programs. Source (18)*

| **FDA: Non-Conformities related to Stability Test programs** |
|---|
| *The written stability testing program is inadequate to assess the stability characteristics of drug products and for determining appropriate storage conditions and expiration dates.* |
| *You have no data to demonstrate that the chemical and physical properties of your products remain acceptable throughout their shelf life.* |

Concerning the WLs issued by EMA, the problem identified was related to stability data, which were incomplete and did not follow local protocols.

### 4.1.4 Microbiological Quality of Raw Material

Microbiological contamination of raw materials was the reason most commonly cited in recalls of non-sterile drug products from the USA market and was mentioned in one recall from the UK market.

In the USA market, raw material contamination was responsible for 57% of recalls of oral solid dosage forms, 29% of recalls of prep pads and 19% of recalls of liquid dosage forms, demonstrating the raw material represents a significant microbial risk to solid dosage forms. To reduce this problem, it is crucial follow cGMP rules and establish microbiological quality control of purified water, API, excipients, container closure systems and any raw material used in the manufacture and packaging of drug products. The GMP requires that each lot of components, drug product containers, and closures

with potential for microbiological contamination, shall be withheld from use until the lot has been sampled, tested, or examined. In addition to quality control tests, the manufacturer should ensure that the excipients and materials are suitable for use in medicinal products and that the suppliers are qualified. (45) (46)

Microbiological quality tests of raw materials are based upon the TAMC, TYMC and the absence of specific microorganisms. The pharmacopoeial monographs determine the limits and acceptable criteria for TAMC and TYMC. (49)

Results from the analysis of WLs showed that microbiological quality of raw material cannot be ensured by many industries that received those WL from FDA or EMA. The most common failures directly related to raw material quality control are presented in Table 45 and Table 46.

*Table 45: FDA - Non-conformities related to raw materials. Source (18)*

| **FDA: Non-conformities related to raw material** |
|---|
| *Your firm failed to test samples of each component for conformity with all appropriate written specifications for purity, strength, and quality.* |
| *Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated.* |
| *Your firm failed to withhold from use each lot of components, drug product containers, and closures until the lot had been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.* |
| *Your firm has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.* |
| *Failure to have a system in place to evaluate suppliers, and failure to adequately test each batch of incoming materials intended to be used in drug production.* |
| *Failure of your quality unit to evaluate raw materials prior to release and use in drug production operations.* |

*Table 46: EMA - Non-conformities related to raw materials. Source (19)*

| **EMA: Non-conformities related to raw material** |
|---|
| *Inadequate control of starting materials - raw materials were observed to be stored at temperatures and relative humidity's significantly outside of their stated requirements.* |
| *Traceability of raw data (HPLC; GC; dissolution test).* |
| *Supplier assurance processes were significantly lacking including compliance with the TSE regulations.* |

These results show that quality control of raw material is absent or is inadequate in industries that receive WL issued by FDA or EMA, and may be the reason for the high number of recalls related to the microbiological contamination of raw material.

The highest scores in RRI obtained with PHA analysis conducted with the collaboration of the ISO committee were attributed to the raw materials quality control. In fact, "failure to establish the reliability of the supplier's analysis through appropriate validation of the supplier test results at appropriate intervals" were classified as moderate risk and received nine scores.

Although classified as a moderate risk, these failures have a considerable impact on Raw material microbiological contamination and recalls of non-sterile drug products.

### 4.1.5 Warning Letters: FDA and EMA

NCs identified on WLs issued by FDA have a different profile from those identified on WLs issued by EMA. However, when classified into 6M categories, they present a similar result. As illustrated in the FDA and EMA Ishikawa diagrams,Figure 12 and Figure 14, "Methods" and "Man Power" were the categories that grouped most of the NCs.

These results mean that inspectors identified problems related to the process performance and the specific requirements for doing it. Lack of scientifically sound procedures, specifications, written testing programs and control procedures were problems frequently cited on WLs and grouped into "Methods" category. As regard to "Man Power" category, the problems identified were mostly related to failures to follow procedures and activities. Therefore, these results point to a lack of training and education on cGMP and show that employees are not able to perform their assigned functions.

Another important similarity observed between WLs issued by FDA and EMA was the high number of non-conformities related to lack of investigation into quality deviation and OOS. Inability to conduct an investigation on deviations implies that the

manufacturers do not know the cause of their problems, thus being unable to solve them. The main differences between FDA and EMA analysis of NC are presented in Table 47. Table 48 and Table 49 show the NC related to investigations pointed by FDA and EMA.

*Table 47: FDA and EMA analysis of WLs. Source (18) (19)*

<table>
<tr><th colspan="3"></th><th>FDA</th><th>EMA</th></tr>
<tr><td rowspan="5">Warning Letters</td><td colspan="2">Total</td><td>143</td><td>112</td></tr>
<tr><td rowspan="2">Sterile</td><td>API</td><td>3%</td><td>4%</td></tr>
<tr><td>Drug Products</td><td>29%</td><td>13%</td></tr>
<tr><td rowspan="2">Non-Sterile</td><td>API</td><td>36%</td><td>58%</td></tr>
<tr><td>Drug Products</td><td>31%</td><td>25%</td></tr>
<tr><td colspan="3" rowspan="3">Most frequently non-conformities committed by industries</td><td>Your firm has not established written production and control procedures to assure that the drug products produced have the identity, strength, quality and purity they purport or are represented to possess. (12%)</td><td>Record integrity and veracity: some records were made up or altered. (9%)</td></tr>
<tr><td>Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (10%)</td><td>There was a continued failure of the Quality Management System and Quality Assurance to establish compliance with EU GMP. (8%)</td></tr>
<tr><td>The written stability testing program is inadequate to assess the stability characteristics of drug products and for determining appropriate storage conditions and expiration dates. (9%)</td><td>Lack of appropriate root causes investigation into deviations. (6%)</td></tr>
</table>

*Table 48: FDA - Non-conformities related to investigations. Source (18)*

| FDA: Non-Conformities related to investigations |
|---|
| *Your firm failed to review and investigate production and QC laboratory deviations.* |
| *Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed.* |
| *Your firm failed to adequately investigate all quality-related complaints.* |
| *Your firm failed to investigate and document out-of-specification results according to a procedure.* |
| *Your firm has not established procedures for investigation of complaints, and for initiation of corrective and preventive actions based on results of such investigation.* |

*Table 49: EMA - Non-conformities related to investigations. Source (19)*

| EMA: Non-Conformities related to investigations |
|---|
| *Lack of appropriate root causes investigation into deviations.* |
| *Inadequate deviations management system with no exhaustive record, no classification and no thorough investigation.* |
| *Failure to raise OOS, related investigations and CAPA.* |

#### 4.1.5.1 *Risk-Ranking Index*

The PHA analysis carried out in collaboration with the ISO committee showed the highest microbiological risks involved in the manufacture of non-sterile drug products. Failures pointed by EMA and FDA during inspection provides information about the reality of many pharmaceutical industries. Thus, the results obtained reflects real scenarios.

RRI developed with NCs from FDA and EMA have crucial differences. Table 50 highlights the main differences observed.

The contrast observed reflect the differences between inspections policies adopted by each one of the agencies. Despite divergent results, they are consistent with reality found in recalls. In fact, all NCs that received the highest score have a direct or indirect influence of microbial contamination.

*Table 50: PHA - FDA and EMA results. Source (18)(19)*

| | | Non-Conformities | |
|---|---|---|---|
| | | **FDA** | **EMA** |
| **Risk-Ranking** | **Low Risk** | 26 NCs | 11 NCs |
| | **Moderate Risk** | 26 NCs | 48 NCs |
| | **High Risk** | 0 NCs | 6 NCs |
| **Top Scores** | **High score obtained** | 9 | 15 |
| | **Numbers of NC** | 3 NCs | 4 NCs |
| **Failures** | | Raw material quality Control | Investigation into deviations |
| | | Control procedures | Cleaning procedures |
| | | Fail to assure the quality of the drug product | Complaint handling |
| | | | Quality Agreements |

#### 4.1.5.2 *Risk-Priority Rank*

FMECA was applied to estimate the risk and develop an RPI. In this way, the risk was defined as a combination of severity, the likelihood of occurrence and difficulty of detection. This tool allowed summarizing the most important NCs and thus highlight the ones that most need attention and efforts.

RPR developed with NCs from FDA and EMA also have crucial differences that are illustrated in Table 51.

*Table 51: FMECA - FDA and EMA results. Source (18) (19)*

| | | Non-Conformities | |
|---|---|---|---|
| | | **FDA** | **EMA** |
| **Risk-Priority** | **1st Priority** | 0 NC | 1 NCs |
| | **2nd Priority** | 1 NC | 11 NCs |
| | **3rd Priority** | 51 NCs | 51 NCs |
| **Top Scores** | **High score obtained** | 27 | 45 |
| | **Numbers of NC** | 1 NC | 1 NC |
| **Failures** | | Control Procedures | Poor Training of operators |
| | | | Investigation into deviations |
| | | | Quality Agreements |

The NCs highlighted are those that receive the worst combination of parameters, using a "low, moderate and high" rating. Therefore, it is prudent spend time, attention and actions to reduce and minimize the failures ranked as 1st or 2nd priority.

## 4.2 Mitigation actions

To reduce the risks listed in this work, mitigation measures should be implemented particularly on high priority hazards. In this way, actions should be taken by both the manufacturer and the regulatory agencies.

Manufacturers of non-sterile drug products should focus their attention on the improvement of the process controls and quality control, especially related to raw material (including API, Water, Excipients, containers, and closures) and stability test programs. A robust design of process and facility and a strict daily operational control is crucial to avoid microbiological contamination, especially fungus and bacteria from genus *Burkholderia*. Rely only on finished product testing is not adequate for controlling microbiological contamination (7).

Regulatory agencies should encourage industries to implement Quality by Design (QbD) into their processes. The QbD principles are essential to define the product's necessary quality attributes. In this way, industries may include TYMC/TAMC and absence of specific bacteria, such as *B. cepacia* as a parameter to be monitored over the manufacturing process and the drug products' life cycle. (7)

Regarding preservative effectiveness, industries should conduct appropriate pre-formulation studies and thoroughly investigate each component of the formulation to avoid any interaction. Another prudent measure is applying a scientifically sound post-market stability study to evaluate if the antimicrobial efficacy remains.

As presented in this work, many of NCs have a direct or indirect effect on microbiological contamination. Therefore, the manufacturer of non-sterile drug products should be alert for the failures pointed, especially those that received the highest score on RRI and Rik-Priority indices.

Accurate information and adequate knowledge of the problem is the key to taking right decisions. In this way, the manufacturer's role is to be attentive to the potential root causes presented in this work and implement actions designed to solve and reduce the problem.

## 5 Conclusion

Regulatory agencies possess large amounts of recall data and detailed inspection reports that are available in their databases. These sources of information allow a cause and effect analysis, as well as the development of a risk-based approach. This work has gathered information on microbiologically related recalls and warning letter issued to a manufacturer of non-sterile finished products to further assess microbiological contamination and develop a risk assessment.

A detailed study of recalls of non-sterile drug products, registered between 2008 and February 2016, allowed the identification of root causes, microorganism responsible for the contamination, characteristics of products most contaminated and the potential impact on patients.

The results obtained showed that microbiological contamination is one of top ten causes of recalls in the US and the UK markets. The microorganisms most cited in all recalls analysed were *B. cepacia* complex (Bcc) and yeasts/molds, and the most cited causes were related to contamination of raw material and failure in preservative effectiveness.

*B. cepacia* was the main microorganisms responsible for contamination of non-sterile drug products in the USA market. The presence of Bcc is closely related to processes involving water or aqueous dosage forms. It is related to the high number of liquid dosage forms recalled in the US, being responsible for the contamination of 45% of liquid dosage forms. In fact, a study on the diversity of bacteria in pharmaceutical water showed that the *Burkholderiaceae* was one of the four bacterial families responsible for 65% of the microbial population (69).

Concerning fungal contamination (yeasts and molds), products designed for nasal or topical application should receive more attention and precaution. The fungal contamination is closely related to a failure in preservative efficacy. The pharmacopoeial AET tests do not permit any increase of mold or yeast from the initial level of inoculation in a test sample containing preservatives.

Raw material contamination was the most cited cause in recalls of non-sterile drug products, clearly indicating failures committed by manufacturers. The analysis conducted on WLs showed that industries do not assure the quality of raw materials used in manufacturing processes. The identified failures were the following: (1) not being able to establish the reliability of the supplier's analysis; (2) failure to evaluate raw materials before releasing to production; and (3) failure to implement a reliable system to evaluate suppliers.

Failure in antimicrobial preservative effectiveness and consequent contamination can be related to many causes, such as the interaction between components of the

formulation, chemical instability, and physical loss or changes. Mitigation of this problem requires robust pre-formulation studies and adequate post-approval market stability test programs.

The study of WLs allowed identifying the most common company failures, as well as the microbiological hazards involved in manufacturing processes. Many NC identified to have a direct or indirect impact on non-sterile drug product recalls. So, the relationship between NC and their possible microbiological effects was studied. Then a PHA and FMECA was conducted to evaluate the risks and to prioritize the mitigation actions.

First, a PHA was applied to studying non-conformities pointed by FDA and EMA, the risk was defined as a combination of the severity of the harm and its likelihood of occurrence. Second, an FMECA was developed and a third parameter, difficulty of detection, introduced in the study. These parameters were determined by a group of 14 representatives of pharmaceutical industries located in Portugal and Infarmed - the ISO committee.

The RRI indices obtained with PHA showed that NC related to the quality of raw material and drug product, and process control received the highest scores in FDA RRI. As regards RRI developed with NC identified by EMA, the highest scores were related to an investigation into deviations, cleaning procedures, complaint handling, and quality agreements.

The RPR developed showed that NC related to training, investigations, and quality agreements are considered the 1st priority to EMA rank. As regard to FDA results, NC related to process control received the highest score and thus was classified as 2nd priority. Results obtained with NC from FDA are less stringent than EMA, although not less important.

For comparison purposes, a second evaluation was developed using the likelihood of occurrence found in WLs issued by FDA and EMA while keeping others parameters defined by ISO group. This approach revealed different results for FDA analysis and similar results for EMA analysis.

This work provides crucial information to manufacturers of non-sterile drug products and regulatory agencies about microbiological contamination and their potential hazards.

With the RRI developed, the manufacturers of non-sterile drug products and the regulatory agencies can implement mitigation actions commensurate with the magnitude of the risk. Microbiological contamination of drug products can be avoided or reduced with science-based initiatives and decisions.

It was also possible to develop a preliminary microbial risk assessment, based on the real situation found in many companies. This work allows the manufacturer to

develop a further analysis and uses more accurate QRM tool to define how these issues can be best prevented, and which are the best mitigation actions that need to be implemented. Pharmaceutical companies should carry their research to establish their microbiological risk and use the data gathered in this study to evaluate their microbial ecology, manufacturing processes, conditions and dosage form characteristics.

## 5.1 Future Work

Where microbial contamination of non-sterile drug product is concerned, it is necessary to further investigate the particularities of process, products and microorganism. It should be possible to evaluate specific dosage forms and analyse each step of the manufacturing process, and its inherent risks.

On the other hand, this study only evaluated recalls from the UK, which does not allow a full assessment of the EU pharmaceutical market, Therefore, to explore in depth the microbiological contamination in EU it will be necessary consult the databases from others regulatory agencies in the EEA.

As shown in the Pareto charts herein developed, ten principal causes are responsible for approximately 80% of recalls of non-sterile drug products in US and UK, most of them being related to failures in the manufacturing process. These findings raise several questions that are still to be answered: Why these recalls happen? What are the reasons for this? Which are the possible risks? Which actions can be implemented to reduce these risks? This thesis demonstrates that all these issues can be suitably evaluated using recalls and warning letters.

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# 7 Annex

*Annex 1: Recalls of non-sterile drug products registered on FDA Enforcement Report. Source (16)*

| Brief description | Dosage form | Date |
|---|---|---|
| Microbial Contamination of Non-Sterile Products; testing revealed out of specification results for total aerobic microbiological count | Topical Spray | 01/27/2016 |
| Microbial Contamination of Non-Sterile Products: Product failed USP Microbial Limits Test. | Wash Kit | 05/20/2015 |
| Does Not Meet Monograph: Products failed the Antimicrobial Effectiveness Test per USP <51> for preservative effectiveness. | Tablets | 04/29/2015 |
| Microbial Contamination of Non-Sterile Products: Lots failed microbiological testing at the 12-month time point. | Oral Solution | 03/25/2015 |
| Microbial Contamination of a Non-Sterile Product: Kit component is contaminated with *Burkholderia multivorans*. | Oral Suspension | 03/18/2015 |
| Microbial Contamination of Non-Sterile Products: Active Pharmaceutical Ingredient (API) failed USP microbial tests. | Topical Solution | 02/18/2015 |
| Microbial Contamination of Non-Sterile Product; microbial assay reported unacceptable high plate counts and positive for *E. Coli* | Oral Spray | 01/01/2015 |
| Microbial Contamination of Non-Sterile Products: Pain Relieving Antiseptic Spray tested positive for microbial growth. | Topical Spray | 11/05/2014 |
| Microbial Contamination of Non-Sterile Products: Consumer complaint confirmed microbial contamination in sales sample. | Tablets | 10/15/2014 |
| Microbial Contamination of Non-Sterile Products: Comfort Shield Barrier Cream Cloth packages tested positive for bacterial contamination. | Cloths (wipes) | 09/10/2014 |
| Microbial Contamination of Non-Sterile Product | Hand Sanitizer | 08/13/2014 |
| Microbial Contamination of Non-Sterile Products: XX recalls six lots due to the presence of mold. | Cream Base | 08/06/2014 |
| Microbial Contamination of Non-Sterile Products: Elevated counts of bacteria was found, *Serratia liquefaciens*. | Hand Sanitizer | 05/14/2014 |
| Microbial Contamination of Non-Sterile Products: Out-of-specification results for microbial count were observed at the initial stability interval for Lansoprazole Delayed-Release Capsules. | Capsules | 03/12/2014 |
| Microbial Contamination of Non-Sterile Products: Fusion Pharmaceuticals recalls the Kit due to Total Yeasts and Molds Count above USP limits. | Oral Suspension | 02/17/2014 |
| Microbial Contamination of Non-Sterile Products: Elevated counts of gram-positive rods were found during environmental testing | Ointment | 02/17/2014 |
| Microbial Contamination of Non-Sterile Product(s): The product was found to be contaminated with Burkholderia sp. | Topical Solution | 02/05/2014 |
| Microbial Contamination of Non-Sterile Products: Arthritis Relief Cream failed microbiological specifications. | Cream Tubes | 01/22/2014 |
| Microbial Contamination of Non-Sterile Products: XX recalls the Phenylephrine Nasal Spray 1% because of possible microbial contamination. | Nasal Spray | 01/01/2014 |
| Microbial Contamination of Non-Sterile Products; Selected lots of Badger Baby and Kids Sunscreen Lotion were recalled due to microbial contamination. | sunscreen | 12/12/2013 |
| Microbial Contamination of Non-Sterile Products: A lot of raw material used in the manufacture of Ranitidine was positive for Pseudomonas sp. | Tablets | 08/21/2013 |
| Microbial Contamination of a Non-Sterile Products: Product was found to be contaminated with the bacteria, *Sarcina Lutea*. | Antimicrobial Hand Soup | 08/21/2013 |
| Microbial Contamination of Non-Sterile Products: This product is being recalled because of a stability sample was found to be contaminated with *Burkholderia contaminants*. | Alcohol prep pads | 07/31/2013 |
| Microbial Contamination of Non-Sterile Products: Lot in question had an elevated microbial count outside of specifications and *E. Coli* contamination. | Oral Solution | 05/08/2013 |
| 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. | Oral Suspension | 04/10/2013 |
| Microbial Contamination of Non-Sterile Product(s): The product has the potential to be contaminated with *Burkholderia gladioli*. | Topical Solution | 03/20/2013 |
| Microbial Contamination of a Non-Sterile Products: 12-Hour Nasal Spray under various labeling are being recalled due to microbial contamination identified during testing. | Nasal Spray | 02/20/2013 |
| Microbial Contamination of Non-Sterile Products: Product may be contaminated with *Burkholderia cepacia*. | Nasal Spray | 02/13/2013 |

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| Microbial Contamination of Non-Sterile Products: The product may be contaminated with bacteria. | Hand Sanitizer | 02/06/2013 |
| Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material. | Limed Bone Gelatin | 11/28/2012 |
| Microbial Contamination of Non-Sterile Products: Laboratory findings of high total plate count above specification. | Hand Sanitizer | 11/07/2012 |
| Microbial Contamination of Non-Sterile Products: Product is being recalled due to possible microbial contamination by *C. difficile* discovered in the raw material. | Capsules | 10/31/2012 |
| Microbial contamination of Non-Sterile Product; contamination with *Burkholderia cepacia* | Alcohol prep pads | 09/26/2012 |
| Microbial Contamination of Non-Sterile Products; Product was found to be contaminated with *Sphingomonas paucimobilis* bacteria. | Mouthwash | 09/05/2012 |
| Microbial Contamination of a Non-Sterile Products: Three product lots are contaminated with *Burkholderia cepacia*. | Mouthwash | 09/05/2012 |
| Microbial Contamination of Non-Sterile Product; mold | Sunscreen | 09/05/2012 |
| Microbial Contamination of Non-Sterile Products; The affected lots were found to be contaminated with a bacterium, *Burkholderia cepacia* complex. | Hand Sanitizer | 07/18/2012 |
| Microbial Contamination of Non-Sterile Product: Simethicone containing products may be contaminated with *B. cepacia* due to a raw material that was used to manufacture the product. | Oral Solution | 04/11/2012 |
| Microbial Contamination of Nonsterile Products: possible contamination with *Burkholderia cepacia.* | Oral Solution | 04/04/2012 |
| Microbial Contamination of Non-Sterile Products: Out of Specification (OOS) result for Purified Water used to rinse product contact parts during manufacturing. | Oral Solution | 03/21/2012 |
| Microbial Contamination of Non-Sterile Products: Product recall due to a potential for microbial (coagulase negative staphylococci) contamination. | Lotion | 03/14/2012 |
| Microbial Contamination of Non-Sterile Products; analysis confirmed that the Ball contains bacteria that may be a potential health risk. | Moisturizing Gel | 02/22/2012 |
| Microbial Contamination of Non-Sterile Products: The Kit contains Povidone Iodine Prep Pads that are being recalled by the Triad Group because they were found to be contaminated with the bacteria, *Elizabethkingia meningoseptica*. | Povidone iodine prep pads | 02/15/2012 |
| Microbial Contamination of Non-Sterile Products: the presence of *Enterobacter gergoviae* and *Pseudomonas monteilii/plecoglossicida.* | Cream tubes | 02/08/2012 |
| Microbial contamination of non-sterile product (gelatin capsules contamination). | Capsules | 01/25/2012 |
| Microbial Contamination of Non-Sterile Products: The mouthwash component of the kit was found to be contaminated with *Burkholderia cepacia.* | Mouthwash | 01/11/2012 |
| Microbial contamination of Non-Sterile Products: Product contaminated with bacteria- *Burkholderia cepacia.* | Hand Sanitizer | 01/04/2012 |
| Microbial Contamination of Non-Sterile Products: Samples of the recalled OTC product were laboratory tested and found to be contaminated with *Burkholderia cepacia*. | Hand Sanitizer | 01/04/2012 |
| Microbial Contamination of Non-Sterile Product; product found to contain *Bulkholderia cepacia.* | Nasal Solution | 12/28/2011 |
| Microbial Contamination of Non-Sterile Product: Various brands of Infant Gas Relief Drops may have microbial contamination with *Burkholderia cepacia* due to a raw material that was used to manufacture the product. | Oral Solution | 12/21/2011 |
| Microbial Contamination of Non-Sterile Products: The convenience kit contained the triptorelin pamoate for injectable suspension products is being recalled because it contains alcohol prep pads manufactured by Triad Group that was previously recalled due to the potential contamination of the pads with the bacteria Bacillus cereus. | Alcohol prep pads | 12/21/2011 |
| Microbial Contamination of Non-Sterile Products: The products contain povidone iodine prep pads which were recalled by the supplier. | Iodine prep pads | 12/21/2011 |
| CGMP Deviations: This kit is being recalled because a component, povidone iodine swab sticks, was recalled by the manufacturer because they were manufactured without having in place a system for microbial testing at the time of release, without having a system for testing of incoming components, and without having procedures designed and established to prevent objectionable microorganisms in drug products. | Povidone iodine prep pads | 11/30/2011 |
| CGMP Deviations: This kit is being recalled because a component, povidone iodine swab sticks, was recalled by the manufacturer because they were manufactured without having in place a system for microbial testing at the time of release, without having a system for testing of incoming components, and without having procedures designed and established to prevent objectionable microorganisms in drug products. | Povidone iodine prep pads | 11/16/2011 |
| Microbial Contamination of Non-Sterile Products: The mouthwash component of the kit was found to be contaminated with *Burkholderia cepacia*. | Mouthwash | 11/09/2011 |
| Microbial Contamination of Non-Sterile Products: The products contain povidone iodine prep pads which were recalled by the supplier. | Povidone iodine prep pads | 11/09/2011 |

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| Microbial Contamination of Non-Sterile Product: This product is being recalled due to the presence of *Burkholderia cepacia* | Nasal Solution | 10/19/2011 |
| Microbial Contamination of Non-Sterile Product: North Safety Kits contain a product component (Triad Alcohol Prep Pads) recalled due to potential *Bacillus cereus*. contamination. | Alcohol prep pads | 10/05/2011 |
| Microbial Contamination of Non-Sterile Product; mold found in gasket area of drum lid. | Simethicone Emulsion | 10/05/2011 |
| Microbial Contamination of Non-Sterile Products: The non-sterile alcohol prep pads/swabs were found to be contaminated with *Bacillus cereus* based on FDA sampling and analysis. | Alcohol prep pads | 10/05/2011 |
| Microbial Contamination of Non-Sterile Products: Products contain povidone iodine prep pads which were recalled by their supplier. | Povidone iodine prep pads | 10/05/2011 |
| Microbial Contamination of Non-Sterile Product: Safety Kits contain a product component (Triad Alcohol Prep Pads) recalled due to potential *Bacillus cereus* contamination. | Alcohol prep pads | 09/28/2011 |
| Microbial Contamination of Non-Sterile Products: kits are being recalled because they may contain potentially contaminated alcohol prep pads which are part of the recent XX Alcohol Prep Pads recall due to potential contamination with the bacteria, *Bacillus cereus*. | Alcohol prep pads | 09/28/2011 |
| Microbial Contamination of Non-Sterile Product; product may be contaminated with *Burkholderia cepacia*. | Oral Solution | 09/21/2011 |
| CGMP Deviations: Products were manufactured without having in place a system for microbial testing at the time of release, without having a system for testing of incoming components, and without having procedures designed and established to prevent objectionable microorganisms in drug products. | Povidone iodine prep pads | 09/14/2011 |
| Microbial Contamination of Non-Sterile Products: This is a sub-recall, Povidine Iodine Prep Pads; The Kits under recall contain Povidine Prep Pads recalled by XX Industries due to the potential contamination with an objectionable organism, *Elizabethkingia meningoseptica*. | Povidone iodine prep pads | 09/07/2011 |
| Microbial Contamination of Non-Sterile Products: Certain lots of the product were confirmed to have exceeded the USP specification for maximum microbial content (microbial type, *Burkholderia Cepacia*). | Simethicone Emulsion | 08/31/2011 |
| Microbial Contamination of Non-Sterile Products: Out of specification results were observed instability sample testing for microbiological limits in three lots of Levetiracetam Oral Solution, 100 mg/ml. | Oral Solution | 08/24/2011 |
| Microbial Contamination of Non-Sterile Products: Certain lots of the product were confirmed to have exceeded the USP specification for maximum microbial content (microbial type, *Burkholderia Cepacia*). | Simethicone Emulsion | 08/10/2011 |
| Microbial Contamination of Non-Sterile Products: Kits are containing Alcohol Prep Pads recalled by XX Industries due to contamination with *Bacillus cereus*. | Alcohol prep pads | 08/03/2011 |
| Microbial Contamination of Non-Sterile Products: XXX has initiated the recall due to recall being conducted for the Triad Povidone Iodine Prep Pads manufactured by XX Industries, Inc. Concerns were expressed by the Food and Drug Administration regarding the potential contamination of Triad Povidone Iodine Prep Pads. The Triad Povidone Iodine Prep Pads are potentially contaminated with an objectionable organism, *Elizabethkingia meningoseptica*. The Triad Povidone Iodine Prep Pads have an NDC number XX and are the only defective material in the First Aid Kits. | Povidone iodine prep pads | 07/27/2011 |
| Microbial contamination of non-sterile products. | Benzalkonium Chloride Swabsticks | 07/13/2011 |
| Microbial Contamination of Non-Sterile Products: The recall of all lots of Povidone Iodine Prep Pads was initiated due to results of analytical testing showing the presence of objectionable organisms, namely showing the presence of objectionable organisms, namely *Staphylococcus warneri*, *Stenotrophomas maltophilia*, and *Elizabethkingia meningoseptica* | Povidone iodine prep pads | 06/08/2011 |
| This action is being taken "due to an abundance of caution" as this product is manufactured by XX Industries XX in the same location which manufactures various sterile alcohol wipes/swabs and swab sticks that are currently being recalled for suspected bacterial contamination. | Alcohol prep pads | 04/20/2011 |
| Microbial contamination of additional brand named Non-Sterile Products: Non-Alcohol Foaming Hand sanitizer may be contaminated with *Burkholderia cepacia*. | Hand Sanitizer | 03/23/2011 |
| Microbial contamination of non-sterile products: kits contain alcohol wipes that have been recalled by xx Group, due to *Bacillus cereus*. | Alcohol prep pads | 03/23/2011 |
| Microbial contamination of non-sterile product; the Kits are being recalled because the alcohol prep pads have the potential to be contaminated with *Bacillus cereus*. | Alcohol prep pads | 03/09/2011 |
| Microbial Contamination of Non-Sterile Products: Kits were manufactured using a recalled component (alcohol pads). | Alcohol prep pads | 03/09/2011 |

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| Microbial contamination; concerns of potential contamination of *Bacillus cereus*. | Alcohol prep pads | 02/14/2011 |
| Microbial Contamination of Non-Sterile Products: FDA testing results identified gram-negative bacteria *Pseudomonas Putida*. | Hand Sanitizer | 11/17/2010 |
| Product may be contaminated with *Burkholderia cepacia*. | Hand Sanitizer | 11/10/2010 |
| Possible microbial contamination | Dietary Supplement | 05/19/2010 |
| Microbial contamination of Non-Sterile products. FDA samples showed contamination with Burkholderia cepacia (a.k.a. *Pseudomonas cepacia*). | Hand Sanitizer | 04/28/2010 |
| Product may be contaminated with *E. coli* | Dietary Supplement | 04/28/2010 |
| The product will not meet its normal shelf life of two years due to the presence of spoilage organisms. | Antimicrobial Hand Soup | 04/14/2010 |
| Error with Regard to Preservative: The lotion has the potential for preservative failure, which would allow mold growth to occur. | Lotion | 03/24/2010 |
| Microbial Contamination of Non-Sterile Product: Product may be contaminated with bacteria *Burkholderia cepacia*. A stability sample had failed microbial content testing. The microbial content was 8560 CFU/ml for the total aerobic count (specification maximum is <100 CFU/ml). | Nasal Spray | 03/10/2010 |
| Pediatric Electrolyte Solution is contaminated with *Pseudomonas fluorescens* and *Serratia fonticola* | Oral Solution | 01/27/2010 |
| Yeast contamination | Oral Suspension | 12/02/2009 |
| Antimicrobial skin sanitizers and hand protectant products may contain high levels of bacteria. | Hand Sanitizer | 11/18/2009 |
| The raw material used to manufacture the finished product may have been contaminated with *B cepacia.* | Oral Suspension | 09/30/2009 |
| Product might not have sufficient preservative levels to inhibit growth of bacteria if organisms introduced post-pasteurization | Dietary Supplement | 08/05/2009 |
| Product may contain the bacteria *Burkholderia cepacia*. | Benzoyl peroxide Gel | 12/10/2008 |
| This product is being recalled due to microbial contamination with *Achromobacter xylosoxidans*, a gram-negative organism. | Topical Solution | 11/12/2008 |
| Product exceeds microbial specifications. | Bacitracin Ointment | 10/29/2008 |
| Product exceeded the microbial limit for Total Aerobic Count, Total Yeast, and Mold Count. | suppository | 10/29/2008 |
| Microbial Contamination of Non-Sterile Product; cloths found to be contaminated with *Burkholderia cepacia* | Cloths (Wipes) | 09/10/2008 |
| CGMP Deviations. The mouthwash was manufactured under conditions whereby it may be contaminated with the bacteria *Burkholderia cepacia*. | Mouthwash | 08/27/2008 |
| Microbial contamination of a non-sterile product. The alcohol-free mouthwash was found to be contaminated with *Burkholderia cepacia* bacteria. | Mouthwash | 08/13/2008 |
| Microbial Contamination of Non-Sterile Product; Yeast. | Oral Solution | 03/12/2008 |

*Annex 2: Non-Conformities identified by FDA, 6M classification, and PHA results. Source (18)*

| Hazards | | ISO group definition of occurrence | | | Likelihood of occurrence found in FDA WLs | | |
|---|---|---|---|---|---|---|---|
| **Non-Conformities** | **6M group** | **Severity** | **Likelihood of Occurrence** | **Risk - Ranking** | **Severity** | **Likelihood of Occurrence** | **Risk - Ranking** |
| 1- Your firm failed to review and investigate production and QC laboratory deviations. | Man Power | 3 | 1 | 3 | 3 | 1 | 3 |
| 2- Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards | Measurements | 3 | 1 | 3 | 3 | 3 | 9 |
| 3- Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity. | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 4-Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed | Man Power | 5 | 1 | 5 | 5 | 5 | 25 |
| 5- You failed to establish written responsibilities and procedures applicable to the quality control unit, including the review of out-of-specification results and customer complaints | Methods | 3 | 1 | 3 | 3 | 1 | 3 |
| 6- Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions | Man Power | 3 | 1 | 3 | 3 | 1 | 3 |
| 7- Your firm failed to establish and follow appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 8- Your firm failed to test samples of each component for conformity with all appropriate written specifications for purity, strength, and quality. | Materials | 3 | 1 | 3 | 3 | 1 | 3 |
| 9- Your firm failed to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data. | Machinery | 3 | 1 | 3 | 3 | 3 | 9 |
| 10- Your firm failed to adequately investigate all quality-related complaints. | Man Power | 3 | 1 | 3 | 3 | 1 | 3 |
| 11- Your firm failed to investigate and document out-of-specification results according to a procedure. | Man Power | 3 | 1 | 3 | 3 | 1 | 3 |
| 12- Component test records specifically associated with batches of drug product manufactured at your facility were not readily available for an authorized inspection during their retention period. | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 13 - Your quality control unit failed to approve procedures and specifications impacting the identity, strength, quality and purity of the drug product. | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |

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|---|---|---|---|---|---|---|---|
| 14 - Your firm has failed to calibrate instruments and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met | Machinery | 3 | 1 | 3 | 3 | 1 | 3 |
| 15 - Your firm failed to withhold from use each lot of components, drug product containers, and closures until the lot had been sampled, tested, or examined, as appropriate, and released for use by the quality control unit | Man Power | 3 | 1 | 3 | 3 | 1 | 3 |
| 16 - The written stability testing program is inadequate to assess the stability characteristics of drug products and for determining appropriate storage conditions and expiration dates | Methods | 5 | 1 | 5 | 5 | 5 | 25 |
| 17- Your firm failed to submit NDA/ANDA Field Alert Reports (FARs) within three working days of receipt of information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 18 - Your firm has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals | Materials | 3 | 3 | 9 | 3 | 1 | 3 |
| 19 - Your firm does not have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release | Methods | 5 | 1 | 5 | 5 | 3 | 15 |
| 20- Your firm neither established nor documented the accuracy, sensitivity, specificity, and/or reproducibility of test methods | Methods | 3 | 1 | 3 | 3 | 1 | 3 |
| 21 - Your firm failed to follow and document at the time of performance required laboratory control mechanisms | Measurements | 1 | 3 | 3 | 1 | 1 | 1 |
| 22 - Your firm has not established separate or defined areas or such other control systems as necessary to prevent contamination or mix-ups during drug manufacturing | Mother Nature | 5 | 1 | 5 | 5 | 1 | 5 |
| 23- Your firm's quality control unit failed to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 24- Your firm failed to ensure that equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size and suitably located to facilitate operations for its intended use and for its cleaning and maintenance | Machinery | 3 | 1 | 3 | 3 | 1 | 3 |
| 25- Your firm has not established written production and control procedures to assure that the drug products produced have the identity, strength, quality and purity they purport or are represented to possess | Methods | 5 | 1 | 5 | 5 | 5 | 25 |
| 26 - You have no data to demonstrate that the chemical and physical properties of your products remain acceptable throughout their (b)(4) shelf life | Measurements | 5 | 1 | 5 | 5 | 1 | 5 |

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|---|---|---|---|---|---|---|---|
| 27 -Your firm failed to follow required laboratory control mechanisms and to record and justify any deviations from them | Measurements | 3 | 1 | 3 | 3 | 1 | 3 |
| 28 - Your firm failed to establish time limits for the completion of each phase of production to assure the quality of the drug product | Methods | 3 | 3 | 9 | 3 | 1 | 3 |
| 29- Your firm failed to reject drug products that did not meet established standards or specifications and any other relevant quality control criteria | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 30 - Your firm failed to establish and follow adequate control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product | Methods | 3 | 3 | 9 | 3 | 1 | 3 |
| 31- Established laboratory control mechanisms are not followed | Measurements | 3 | 1 | 3 | 3 | 1 | 3 |
| 32 - Your firm failed to establish and follow adequate written procedures for the preparation of master production and control records designed to assure uniformity from batch to batch | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 33 - Your firm has not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product | Machinery | 5 | 1 | 5 | 5 | 1 | 5 |
| 34 - Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 35 - Your firm failed to maintain adequate written records of major equipment maintenance | Measurements | 3 | 1 | 3 | 3 | 1 | 3 |
| 36 - You failed to test finished batches of your drug products for the identity and strength of active ingredients | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 37 - Failure to assign and identify raw materials with a distinctive code, batch, or receipt number, and to identify the disposition of materials. | Materials | 5 | 1 | 5 | 5 | 1 | 5 |
| 38 - Your firm also failed to establish acceptance criteria for the sampling and testing conducted by the quality control unit that is adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 39 -Your firm fails to follow written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products. These procedures shall incorporate the identification of the drug product with a lot or control number that permits the determination of the history of the manufacture and control of the batch | Methods | 3 | 1 | 3 | 3 | 1 | 3 |
| 40 - Your firm failed to ensure that employees received training in current good manufacturing practices, as well as in particular operations assigned to the employees | Man Power | 3 | 1 | 3 | 3 | 1 | 3 |
| 41 - Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. | Man Power | 3 | 1 | 3 | 3 | 1 | 3 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 42 - Your firm failed to maintain written production, control, or distribution records specifically associated with a batch of a drug product for at least one year after the expiration date of the batch | Measurements | 1 | 1 | 1 | 1 | 1 | 1 |
| 43 - Your firm failed to establish and follow written procedures to evaluate, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures | Methods | 3 | 1 | 3 | 3 | 1 | 3 |
| 44 - Your firm has not established and documented the accuracy, reliability and performance of your computer systems employed in the release of drug products | Machinery | 3 | 1 | 3 | 3 | 1 | 3 |
| 45 - Written procedures are lacking that describe in sufficient detail the receipt, identification, storage, handling, sampling, testing, approval, rejection of components, drug product containers, and closures. Bagged or boxed components of drug product containers and closures are not stored off the floor and are not suitably spaced to allow cleaning and inspection | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 46 - Your firm failed to routinely calibrate, inspect, or check according to a written program designed to assure proper performance and to maintain adequate written records of calibration checks and inspections of automatic, mechanical, electronic equipment, or other types of equipment, including computers, used in the manufacture, processing, packing, and holding of a drug product | Machinery | 3 | 1 | 3 | 3 | 1 | 3 |
| 47 - Failure to have a system in place to evaluate suppliers, and failure to adequately test each batch of incoming materials intended to be used in drug production. | Materials | 3 | 1 | 3 | 3 | 1 | 3 |
| 48 - Your firm failed to conduct at least one specific identity test on a component when relying on that component supplier's analysis | Materials | 3 | 1 | 3 | 3 | 1 | 3 |
| 49- Failure of your quality unit to evaluate raw materials prior to release and use in drug production operations. | Materials | 5 | 1 | 5 | 5 | 1 | 5 |
| 50 - Your quality control unit has not approved or rejected all procedures or specifications impacting the identity, strength, quality, and purity of the drug product; all procedures applicable to the quality control unit are not in writing, and all procedures are not followed | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 51 - Your firm failed to prepare batch production and control records for each batch of drug product that includes documentation of the accomplishment of each significant step in the manufacture, processing, packing, or holding of the batch | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 52 - Your firm has not established procedures for investigation of complaints, and for initiation of corrective and preventive actions based on results of such investigation | Methods | 3 | 1 | 3 | 3 | 1 | 3 |

*Annex 3: FMECA results – FDA Risk-Priority Rank. Source (18)*

| Hazards | ISO group definition of occurrence | | | | Likelihood of occurrence found in FDA WLs | | | |
|---|---|---|---|---|---|---|---|---|
| **Non-Conformities** | **Severity** | **Likelihood of Occurrence** | **Difficulty of detection** | **Risk - Priority** | **Severity** | **Likelihood of Occurrence** | **Difficulty of detection** | **Risk - Priority** |
| 1- Your firm failed to review and investigate production and QC laboratory deviations. | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 2- Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards | 3 | 1 | 1 | 3 | 3 | 3 | 1 | 9 |
| 3- Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 4-Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed | 5 | 1 | 1 | 5 | 5 | 5 | 1 | 25 |
| 5- You failed to establish written responsibilities and procedures applicable to the quality control unit, including the review of out-of-specification results and customer complaints | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 6- Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions | 3 | 1 | 3 | 9 | 3 | 1 | 3 | 9 |
| 7- Your firm failed to establish and follow appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 8- Your firm failed to test samples of each component for conformity with all appropriate written specifications for purity, strength, and quality. | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 9-Your firm failed to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data. | 3 | 1 | 3 | 9 | 3 | 3 | 3 | 27 |
| 10- Your firm failed to adequately investigate all quality-related complaints. | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 11- Your firm failed to investigate and document out-of-specification results according to a procedure. | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 12- Component test records specifically associated with batches of drug product manufactured at your facility were not readily available for an authorized inspection during their retention period. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 13 - Your quality control unit failed to approve procedures and specifications impacting the identity, strength, quality and purity of the drug product. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 14 - Your firm has failed to calibrate instruments and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 15 - Your firm failed to withhold from use each lot of components, drug product containers, and closures until the lot had been sampled, tested, or examined, as appropriate, and released for use by the quality control unit | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 16 - The written stability testing program is inadequate to assess the stability characteristics of drug products and for determining appropriate storage conditions and expiration dates | 5 | 1 | 1 | 5 | 5 | 5 | 1 | 25 |
| 17- Your firm failed to submit NDA/ANDA Field Alert Reports (FARs) within three working days of receipt of information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 18 - Your firm has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals | 3 | 3 | 1 | 9 | 3 | 1 | 1 | 3 |
| 19 - Your firm does not have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release | 5 | 1 | 1 | 5 | 5 | 3 | 1 | 15 |
| 20- Your firm neither established nor documented the accuracy, sensitivity, specificity, and/or reproducibility of test methods | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 21 - Your firm failed to follow and document at the time of performance required laboratory control mechanisms | 1 | 3 | 1 | 3 | 1 | 1 | 1 | 1 |
| 22 - Your firm has not established separate or defined areas or such other control systems as necessary to prevent contamination or mix-ups during drug manufacturing | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 23- Your firm's quality control unit failed to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 24- Your firm failed to ensure that equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size and suitably located to facilitate operations for its intended use and for its cleaning and maintenance | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 25- Your firm has not established written production and control procedures to assure that the drug products produced have the identity, strength, quality and purity they purport or are represented to possess | 5 | 1 | 1 | 5 | 5 | 5 | 1 | 25 |
| 26 - You have no data to demonstrate that the chemical and physical properties of your products remain acceptable throughout their (b)(4) shelf life | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 27 -Your firm failed to follow required laboratory control mechanisms and to record and justify any deviations from them | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 28 - Your firm failed to establish time limits for the completion of each phase of production to assure the quality of the drug product | 3 | 3 | 1 | 9 | 3 | 1 | 1 | 3 |
| 29- Your firm failed to reject drug products that did not meet established standards or specifications and any other relevant quality control criteria | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 30 - Your firm failed to establish and follow adequate control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product | 3 | 3 | 3 | 27 | 3 | 1 | 3 | 9 |
| 31- Established laboratory control mechanisms are not followed | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 32 - Your firm failed to establish and follow adequate written procedures for the preparation of master production and control records designed to assure uniformity from batch to batch | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 33 - Your firm has not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 34 - Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 35 - Your firm failed to maintain adequate written records of major equipment maintenance | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 36 - You failed to test finished batches of your drug products for the identity and strength of active ingredients | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 37 - Failure to assign and identify raw materials with a distinctive code, batch, or receipt number, and to identify the disposition of materials. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 38 - Your firm also failed to establish acceptance criteria for the sampling and testing conducted by the quality control unit that is adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 39 -Your firm fails to follow written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products. These procedures shall incorporate the identification of the drug product with a lot or control number that permits the determination of the history of the manufacture and control of the batch | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 40 - Your firm failed to ensure that employees received training in current good manufacturing practices, as well as in particular operations assigned to the employees | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 41 - Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 42 - Your firm failed to maintain written production, control, or distribution records specifically associated with a batch of a drug product for at least one year after the expiration date of the batch | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 43 - Your firm failed to establish and follow written procedures to evaluate, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures | 3 | 1 | 3 | 9 | 3 | 1 | 3 | 9 |
| 44 - Your firm has not established and documented the accuracy, reliability and performance of your computer systems employed in the release of drug products | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 45 - Written procedures are lacking that describe in sufficient detail the receipt, identification, storage, handling, sampling, testing, approval, rejection of components, drug product containers, and closures. Bagged or boxed components of drug product containers | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| and closures are not stored off the floor and are not suitably spaced to allow cleaning and inspection | | | | | | | | |
| 46 - Your firm failed to routinely calibrate, inspect, or check according to a written program designed to assure proper performance and to maintain adequate written records of calibration checks and inspections of automatic, mechanical, electronic equipment, or other types of equipment, including computers, used in the manufacture, processing, packing, and holding of a drug product | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 47 - Failure to have a system in place to evaluate suppliers, and failure to adequately test each batch of incoming materials intended to be used in drug production. | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 48 - Your firm failed to conduct at least one specific identity test on a component when relying on that component supplier's analysis | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 49- Failure of your quality unit to evaluate raw materials prior to release and use in drug production operations. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 50 - Your quality control unit has not approved or rejected all procedures or specifications impacting the identity, strength, quality, and purity of the drug product; all procedures applicable to the quality control unit are not in writing, and all procedures are not followed | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 51 - Your firm failed to prepare batch production and control records for each batch of drug product that includes documentation of the accomplishment of each significant step in the manufacture, processing, packing, or holding of the batch | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 52 - Your firm has not established procedures for investigation of complaints, and for initiation of corrective and preventive actions based on results of such investigation | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |

*Annex 4: Non-Conformities identified by EMA, 6M classification, and PHA results. Source (19)*

| Hazards | | ISO group definition of occurrence | | | Likelihood of occurrence found in EMA WLs | | |
|---|---|---|---|---|---|---|---|
| **Non-Conformities** | **6M group** | **Severity** | **Likelihood of Occurrence** | **Risk - Ranking** | **Severity** | **Likelihood of Occurrence** | **Risk - Ranking** |
| 01- Quality Control deficiencies including: inadequate records. | Measurements | 5 | 1 | 5 | 5 | 1 | 5 |
| 02- There was a continued failure of the Quality Management System and Quality Assurance to establish compliance with EU GMP. | Man Power | 5 | 1 | 5 | 5 | 5 | 25 |
| 03- Failure to raise OOS, related investigations, and CAPA. | Man Power | 5 | 3 | 15 | 5 | 3 | 15 |
| 04- Record integrity and veracity: some records were made up or altered. | Measurements | 5 | 1 | 5 | 5 | 5 | 25 |
| 05- Testing of raw materials and finished products was not conducted in accordance with the principle of GQCLP. | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 06- Deficiencies were related to the poor training of operators especially temporary operators and the absence of adequate documentation. | Man Power | 3 | 3 | 9 | 3 | 1 | 3 |
| 07- A failure to effectively address the deficiencies cited at the previous inspection. | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 08 - Deficiencies were related to equipment: the maintenance and qualification of equipment were not satisfactory as equipment showed an excessive wear and degradation including rust. | Machinery | 5 | 1 | 5 | 5 | 1 | 5 |
| 09- Critical deficiency. There was no comprehensively designed and correctly implemented system of Quality Assurance that was fully documented and adequately resourced with competent personnel and suitable equipment. | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 10 - The major deficiencies related to batch certification. | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 11- lack of robust product review. | Methods | 3 | 3 | 9 | 3 | 1 | 3 |
| 12- Lack of appropriate root cause investigation into deviations. | Man Power | 3 | 3 | 9 | 3 | 3 | 9 |
| 13- One manufacturing process has not been revalidated after severe process changes (frequent quality defects of this product have been reported to the inspectorate ). | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 14- Stability data was incomplete and did not follow local protocols. | Methods | 3 | 1 | 3 | 3 | 1 | 3 |
| 15 - There was a significant risk of contamination within the oral solids manufacturing block. The risk arose from ingress of flies, poor facility maintenance and dust collection from vacuum dust collector outlets which were in close proximity to HVAC inlets. | Mother Nature | 5 | 1 | 5 | 5 | 1 | 5 |
| 16- Traceability of raw data (HPLC; GC; dissolution test). | Measurements | 5 | 1 | 5 | 5 | 1 | 5 |
| 17- Deficiencies were related to the premises which were poorly maintained associated with a deficient pest control. Different areas, where products and cleaned equipment were exposed, were not supplied by filtered air. | Mother Nature | 5 | 1 | 5 | 5 | 1 | 5 |
| 18- Doesn't have quality control manager and a qualified person. | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 19 - Deficiency was related to documentation and control. | Methods | 3 | 1 | 3 | 3 | 1 | 3 |
| 20- the Poor level of control on starting materials supply. | Materials | 5 | 1 | 5 | 5 | 1 | 5 |
| 21- Product impact assessments failed to ensure that the defective product was not potentially supplied to the user. | Materials | 5 | 1 | 5 | 5 | 1 | 5 |
| 22- Inadequate deviations management system with no exhaustive record, no classification, and no thorough investigation. | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 23 - The company failed to prove that all relevant analytical methods used have been validated by the QC department. | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 24 - Quality Control deficiencies including lack of specificity in analytical methods. | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 25- Inappropriate validation of cleaning procedures. | Machinery | 5 | 3 | 15 | 5 | 1 | 5 |
| 26- A major deficiency regarding the change control program (not all changes were controlled appropriately). | Methods | 3 | 1 | 3 | 3 | 1 | 3 |
| 27- Doesn't have equipment for quality control complying with Good Manufacturing Practice requirements. | Machinery | 5 | 1 | 5 | 5 | 1 | 5 |
| 28 - Poorly designed water system. | Materials | 5 | 1 | 5 | 5 | 1 | 5 |
| 29- Doesn't have control and storage complying with Good Manufacturing Practice requirements. | Mother Nature | 5 | 1 | 5 | 5 | 1 | 5 |
| 30 - Dispensary operations did not ensure that the items were dispensed using appropriate weighing equipment, the dispensing activity was accurately recorded, and cross contamination was prevented. | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 31- Failure to notify competent authorities on the discovery of defective products. | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 32- Inappropriate reference material has been used – the company could not deliver proof that the current reference material is suitable for the intended use. | Materials | 5 | 1 | 5 | 5 | 1 | 5 |
| 33- Documentation - quality system elements/procedures. | Methods | 3 | 1 | 3 | 3 | 1 | 3 |
| 34- Failures in line clearance. | Measurements | 5 | 1 | 5 | 5 | 1 | 5 |
| 35- Poor in-process control is handling (weight of vials, the weight of tablets and hard capsules). | Measurements | 3 | 1 | 3 | 3 | 1 | 3 |
| 36 - Data falsification in relation to training records which were rewritten without authorization. | Measurements | 5 | 1 | 5 | 5 | 1 | 5 |
| 37- Deficiency was related to the insufficient microbiological monitoring of the production areas. | Measurements | 5 | 1 | 5 | 5 | 1 | 5 |
| 38 - Lack of some analytical methods. | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 39- Failure in some validation activities including technology transfer. | Man Power | 3 | 1 | 3 | 3 | 1 | 3 |
| 40- Documents not correctly distributed and maintained. | Methods | 3 | 1 | 3 | 3 | 1 | 3 |
| 41- Self-inspection is not addressing adequately the situation (no comment on the excessive degradation of premises and equipment in the last reports). | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 42- Lack of validation for IT system used for storage and laboratory activities. | Machinery | 3 | 1 | 3 | 3 | 1 | 3 |
| 43- Deficiency was related to the environmental control. | Measurements | 3 | 1 | 3 | 3 | 1 | 3 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 44- Deficiency was related to the Quality control. | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 45- Production practices did not meet the specifications described in authorized CTD. CTDs were not updated regard the actual operation activities. | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 46- Deficiency was related to Complaint handling. | Man Power | 5 | 3 | 15 | 5 | 1 | 5 |
| 47- Quality Agreements for production on behalf of Third Parties were not updated. | Man Power | 5 | 3 | 15 | 5 | 1 | 5 |
| 48- Many standard operating procedures did not meet GMP requirements. | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 49 -Validation of analytical methods were not robust and failed to ensure that equipment and processes were appropriately qualified. | Methods | 3 | 1 | 3 | 3 | 1 | 3 |
| 50 - Deficiencies were related to production with a poor cleaning of production equipment, an unsatisfactory handling of cleaned/ uncleaned status resulting in a risk of cross contamination or mix-up. | Machinery | 5 | 1 | 5 | 5 | 1 | 5 |
| 51- Defective performance of cleaning, lack of effective supervision of cleaning and housekeeping. | Mother Nature | 5 | 1 | 5 | 5 | 1 | 5 |
| 52- Doesn't have production equipment complying with Good Manufacturing Practice requirements. | Machinery | 5 | 1 | 5 | 5 | 1 | 5 |
| 53- Deficiency was related to design and maintenance of equipment. | Machinery | 5 | 1 | 5 | 5 | 1 | 5 |
| 54- Inadequate control of starting materials - raw materials were observed to be stored at temperatures and relative humidity's significantly outside of their stated requirements. | Materials | 5 | 1 | 5 | 5 | 1 | 5 |
| 55- Doesn't have premises for production complying with Good Manufacturing Practice requirements. | Mother Nature | 5 | 1 | 5 | 5 | 1 | 5 |
| 56- Deficiency was related to design and maintenance of premises. | Mother Nature | 5 | 1 | 5 | 5 | 1 | 5 |
| 57- There was the risk of contamination and cross-contamination of products due to general system failures, lack of appropriate risk assessment upon new product introduction. | Methods | 5 | 1 | 5 | 5 | 1 | 5 |
| 58- Deficiency was related to Management responsibility. | Man Power | 3 | 1 | 3 | 3 | 1 | 3 |
| 59- Supplier Assurance processes were significantly lacking including compliance with the TSE regulations. | Materials | 5 | 1 | 5 | 5 | 1 | 5 |
| 60- Technical and organizational methods were insufficient to prevent cross contamination. | Mother Nature | 5 | 1 | 5 | 5 | 1 | 5 |
| 61- Document records did not provide a history which was reflective of processes or products. | Measurements | 5 | 1 | 5 | 5 | 1 | 5 |
| 62- Deficiency was related to personnel issues: Hygiene/Clothing. | Man Power | 5 | 1 | 5 | 5 | 1 | 5 |
| 63- The manufacturer has not established a quality management system including adequate controls to ensure the accuracy and completeness of the critical records data. | Measurements | 5 | 1 | 5 | 5 | 1 | 5 |

*Annex 5: FMECA results – EMA Risk-Priority Rank (19)*

| Hazards | ISO group definition of occurrence | | | | Likelihood of occurrence found in EMA WLs | | | |
|---|---|---|---|---|---|---|---|---|
| **Non-Conformities** | **Severity** | **Likelihood of Occurrence** | **Difficulty of detection** | **Risk - Priority** | **Severity** | **Likelihood of Occurrence** | **Difficulty of detection** | **Risk - Priority** |
| 01- Quality Control deficiencies including: inadequate records. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 02- There was a continued failure of the Quality Management System and Quality Assurance to establish compliance with EU GMP. | 5 | 1 | 1 | 5 | 5 | 5 | 1 | 25 |
| 03- Failure to raise OOS, related investigations and CAPA. | 5 | 3 | 1 | 15 | 5 | 3 | 1 | 15 |
| 04- Record integrity and veracity: some records were made up or altered. | 5 | 1 | 3 | 15 | 5 | 5 | 3 | 75 |
| 05- Testing of raw materials and finished products was not conducted in accordance with the principle of GQCLP. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 06- Deficiencies were related to the poor training of operators especially temporary operators and the absence of adequate documentation. | 3 | 3 | 3 | 27 | 3 | 1 | 3 | 9 |
| 07- A failure to effectively address the deficiencies cited at the previous inspection. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 08 - Deficiencies were related to equipment: the maintenance and qualification of equipment were not satisfactory as equipment showed an excessive wear and degradation including rust. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 09- Critical deficiency. There was no comprehensively designed and correctly implemented system of Quality Assurance that was fully documented and adequately resourced with competent personnel and suitable equipment. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 10 - The major deficiencies related to batch certification. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 11- lack of robust product review. | 3 | 3 | 1 | 9 | 3 | 1 | 1 | 3 |
| 12- Lack of appropriate root cause investigation into deviations. | 3 | 3 | 3 | 27 | 3 | 3 | 3 | 27 |
| 13- One manufacturing process has not been revalidated after severe process changes (frequent quality defects of this product have been reported to the inspectorate ). | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 14- Stability data was incomplete and did not follow local protocols. | 3 | 1 | 3 | 9 | 3 | 1 | 3 | 9 |
| 15 - There was a significant risk of contamination within the oral solids manufacturing block. The risk arose from ingress of flies, poor facility maintenance and dust collection from vacuum dust collector outlets which were in close proximity to HVAC inlets. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 16- Traceability of raw data (HPLC; GC; dissolution test). | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 17- Deficiencies were related to the premises which were poorly maintained associated with a deficient pest control. Different areas, where products and cleaned equipment were exposed, were not supplied by filtered air. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 18- Doesn't have quality control manager and a qualified person. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 19 - Deficiency was related to documentation and control. | 3 | 1 | 3 | 9 | 3 | 1 | 3 | 9 |
| 20- Poor level of control on starting materials supply. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 21- Product impact assessments failed to ensure that the defective product was not potentially supplied to the user. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 22- Inadequate deviations management system with no exhaustive record, no classification and no thorough investigation. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 23 - The company failed to prove that all relevant analytical methods used have been validated by the QC department. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 24 - Quality Control deficiencies including: lack of specificity in analytical methods. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 25- Inappropriate validation of cleaning procedures. | 5 | 3 | 1 | 15 | 5 | 1 | 1 | 5 |
| 26- A major deficiency regarding the change control program (not all changes were controlled appropriately). | 3 | 1 | 3 | 9 | 3 | 1 | 3 | 9 |
| 27- Doesn't have equipment for quality control complying with Good Manufacturing Practice requirements. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 28 - Poorly designed water system. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 29- Doesn't have control and storage complying with Good Manufacturing Practice requirements. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 30 - Dispensary operations did not ensure that the items were dispensed using appropriate weighing equipment, the dispensing activity was accurately recorded, and cross contamination was prevented. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 31- Failure to notify competent authorities on the discovery of defective products. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 32- Inappropriate reference material has been used – the company could not deliver proof that the current reference material is suitable for the intended use. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 33- Documentation - quality system elements/procedures. | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 34- Failures in line clearance. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 35- Poor in-process control is handling (weight of vials, the weight of tablets and hard capsules). | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 36 - Data falsification in relation to training records which were rewritten without authorization. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |

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| 37- Deficiency was related to the insufficient microbiological monitoring of the production areas. | 5 | 1 | 3 | 15 | 5 | 1 | 3 | 15 |
| 38 - Lack of some analytical methods. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 39- Failure in some validation activities including technology transfer. | 3 | 1 | 3 | 9 | 3 | 1 | 3 | 9 |
| 40- Documents not correctly distributed and maintained. | 3 | 1 | 3 | 9 | 3 | 1 | 3 | 9 |
| 41- Self-inspection is not addressing adequately the situation (no comment on the excessive degradation of premises and equipment in the last reports). | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 42- Lack of validation for IT system used for storage and laboratory activities. | 3 | 1 | 3 | 9 | 3 | 1 | 3 | 9 |
| 43- Deficiency was related to the environmental control. | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 44- Deficiency was related to the Quality control. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 45- Production practices did not meet the specifications described in authorized CTD. CTDs were not updated regard the actual operation activities. | 5 | 1 | 3 | 15 | 5 | 1 | 3 | 15 |
| 46- Deficiency was related to Complaint handling. | 5 | 3 | 1 | 15 | 5 | 1 | 1 | 5 |
| 47- Quality Agreements for production on behalf of Third Parties were not updated. | 5 | 3 | 3 | 45 | 5 | 1 | 3 | 15 |
| 48- Many standard operating procedures did not meet GMP requirements. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 49 -Validation of analytical methods were not robust and failed to ensure that equipment and processes were appropriately qualified. | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 50 - Deficiencies were related to production with a poor cleaning of production equipment, an unsatisfactory handling of cleaned/ uncleaned status resulting in a risk of cross contamination or mix-up. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 51- Defective performance of cleaning, lack of effective supervision of cleaning and housekeeping. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 52- Doesn't have production equipment complying with Good Manufacturing Practice requirements. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 53- Deficiency was related to design and maintenance of equipment. | 5 | 1 | 3 | 15 | 5 | 1 | 3 | 15 |
| 54- Inadequate control of starting materials - raw materials were observed to be stored at temperatures and relative humidity's significantly outside of their stated requirements. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 55- Doesn't have premises for production complying with Good Manufacturing Practice requirements. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 56- Deficiency was related to design and maintenance of premises. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |

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| 57- There was the risk of contamination and cross-contamination of products due to general system failures, lack of appropriate risk assessment upon new product introduction. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 58- Deficiency was related to Management responsibility. | 3 | 1 | 1 | 3 | 3 | 1 | 1 | 3 |
| 59- Supplier Assurance processes were significantly lacking including compliance with the TSE regulations. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 60- Technical and organizational methods were insufficient to prevent cross contamination. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 61- Document records did not provide a history which was reflective of processes or products. | 5 | 1 | 1 | 5 | 5 | 1 | 1 | 5 |
| 62- Deficiency was related to personnel issues: Hygiene/Clothing. | 5 | 1 | 3 | 15 | 5 | 1 | 3 | 15 |
| 63- The manufacturer has not established a quality management system including adequate controls to ensure the accuracy and completeness of the critical records data. | 5 | 1 | 3 | 15 | 5 | 1 | 3 | 15 |