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# Microbial Contamination in Controlled Environments: Industry Trends and Prevention Methods

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## Abstract

cGMP deficiencies as it pertains to microbial quality in pharmaceutical manufacturing environments tend to monopolize the number of regulatory observations in the industry. Finding a balance between practicality and the business needs of individual firms and regulatory and compliance expectations continues to be a challenge. A review of the 2018 warning letters given by the FDA in the category of 'manufacturing quality' reveal a common thread among pharmaceutical firms; minimal priority placed on controlling the entry of microorganisms into the manufacturing environment and a lack of proactive measures to prevent future excursions. This short review attempts to reveal in a concise manner the challenges that the pharmaceutical industry faces when producing sterile products while trying to work within the confines of regulatory and compliance expectations and some practical suggestions by members of the industry on how to find balance between what is feasible and what is compliant by encouraging [microbial] quality by design into the manufacturing process.

***Keywords:*** *cGMP; Pharmaceutical Manufacturing; Microbial Quality; FDA; Compliance; QbD*

## Introduction

This paper summarizes both sterile and non-sterile drug product contamination case studies evidenced by FDA warning letters under the category of Manufacturing Quality by the Center for Drug Evaluation and Research, 2018 and applicable literature accounts of microbial contamination in controlled environments. cGMP deficiencies, industry trending with a particular focus on Microbiological Quality and key parameters of a well-designed and functioning quality system are discussed. Commonly occurring themes include but are not limited to: the failure to assess the quality of each batch purported to be sterile and the failure to establish and validate written procedures. Part of the problem appears to be a general lack of understanding of the science of Microbiology where it is applied to the Pharma manufacturing environments. Additionally, a lack of understanding of how microorganisms can breach and impact the manufacturing process and ultimately, the product appears to be a contributing factor to the deficiencies seen in the category of manufacturing quality. Contamination prevention in controlled environments producing pharmaceutical products is paramount so, professionals with training in Microbiology are key to the success of such a program. It is also noted that one common recommendation by the Agency is for companies to seek assistance from cGMP consultants. Though the advice of a consultant is undoubtedly value added, it would be even more valuable for each firm to have as a permanent part of their quality team, a trained Microbiologist who can apply the science to the manufacturing environment and can assist in the development of a quality program that would best suit the needs of the organization.

## Methodology

Deficiencies seen in Pharmaceutical Manufacturing were researched using FDA/CDER Manufacturing Quality warning letters for the year 2018 [1]. The focus was on those area(s) that prove themselves most problematic for industry when trying to maintain [microbial]

quality of their manufacturing environments. Additionally, literature searches were conducted focusing on 'lessons learned' by the Pharma industry when addressing microbial excursions. FDA warning letters were chosen to give the best indicator of the Agency's focus when auditing pharmaceutical companies for quality in the manufacturing processes. It is believed that this strategy will give the Pharma industry focused insight on those areas that the FDA believes to be problematic and reoccurring when assessing the [microbial] quality of processes and environment. It is hoped that this information will enable industry to design their processes with [microbial] quality in mind (QbD).

## Key observations

In reviewing 30 warning letters issued by the Division of Manufacturing Quality, CDER, FDA, it is noted that the most common trends in citations tend to be focused on lack of validated procedures that have been designed to prevent microbial contamination, ensuring that there are robust and scientifically sound testing methods to assure conformance and the failure to thoroughly investigate the failure of a batch and determine the root cause of the failure [1].

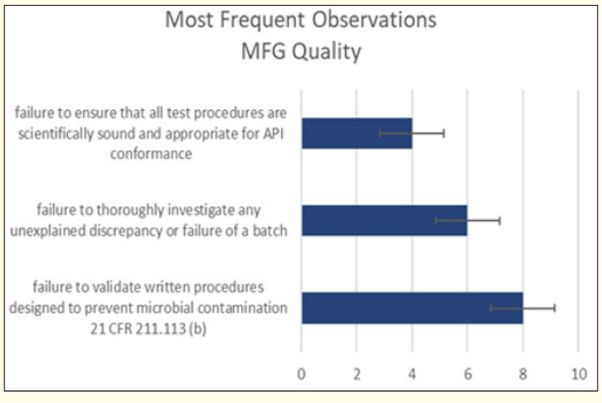


***Figure 1***

Without adequate testing procedures to address conformance, it is impossible to sufficiently address [microbial control] of the manufacturing environment. Not only do the testing procedures need to be robust and challenged for specificity, reproducibility, sensitivity etc., they must also be validated and focusses on the prevention or at least, minimizing the chances of microbial contamination of processes and environment. When excursions happen, it is important to investigate and identify the root cause of any batch failure. This information allows for the 'fine tuning' of the manufacturing process; taking into account the failure, so as to prevent its reoccurrence.

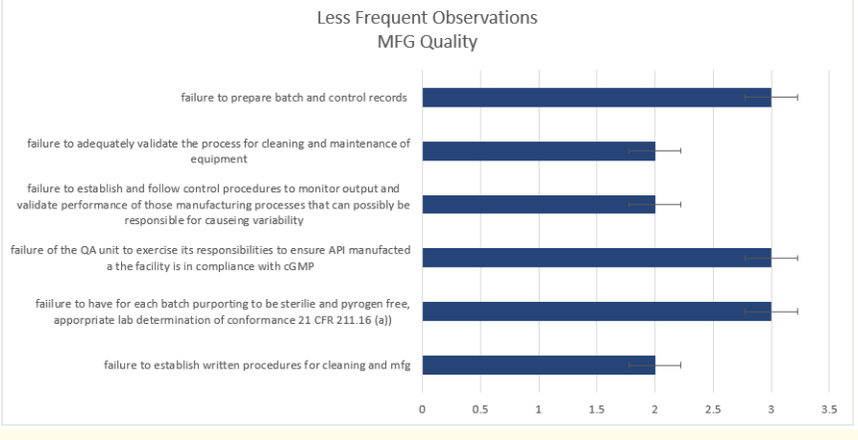


***Figure 2***

Those observations that appeared less frequently when reviewing 2018 Warning Letters, though significant in impact to [microbial] quality, is more related to preventative measures to ensure continued control of the manufacturing environment. It is critical to any pharmaceutical manufacturing environment to prepare and maintain batch records for each and every batch produced. It is impossible to track, trend or troubleshoot without such documentation in existence. The fact that the Agency is citing firms on: the lack of documentation to show that there are appropriate lab controls in place to support claims of sterility and or pyrogen free, the lack or written procedures for cleaning and disinfection as well as the associated validations are a testament to how important this information is to demonstrate 'safe and efficacious use' of the resulting product.

## Industry 'pulse' and the literature

In reviewing the literature, several firms have taken the initiative to find practical ways to gain and maintain control over their manufacturing environments. The focus is comprehensive in nature spanning formulation, components, containers and closures, equipment and storage. All of the above have limits to which endotoxin levels can exceed and cause problems. All depyogentation processes must be validated for the reduction/removal of endotoxin. While others have determined that hold times should be established via reproducible studies while suggesting that fill processes should be assessed for the following: how long a non-sterile batch can be held prior to filtration, how long a sterile solution can be held prior to filling, how long sterilized equipment can be held prior to its use and how long sterilize containers and closures can be held prior to use [2].

When establishing and validating hold times for example, the following should be considered: low risk compounding- measures operator aseptic technique, medium risk compounding addresses larger volumes (100 mL) of sterile media transferred aseptically by gravity into empty containers and high-risk compounding focusses on non-sterile media is used where procedure involves both aseptic transfers and the use of 'in-line' sterilization filters to transfer media into sterile vials. After initial qualification-media fills are conducted on a periodic basis ~ 2X yearly on the same filling line [2].

When assessing the manufacturing environment itself, it is suggested that alert and action limits must also be established based on the relationship of the monitoring location and critical operation. Individual results that exceed the alert limit should focus on trending and historical data and associated MFG deviations of that particular environment. Results that exceed the action limit must prompt a thorough with cleaning and disinfection efficacy assessed by environmental monitoring [2].

The practicality of identifying every isolate on all EM plates is being challenged across industry. The suggestion is that it would be to characterize the isolates when establishing the relationship of those isolates to the manufacturing environment. This information allows the organization to decide what organisms are truly 'objectionable' based on the historical bioburden of that specific environment. Low level contamination presents challenges because it is not always detected as a result of false negatives during monitoring. Therefore, consecutive growth results should not be considered the only type of adverse trend. Recommended to observe the increase in evidence of contamination over a given period of time [2]. Another concern in the pharmaceutical manufacturing environment is the contamination risk in lyophilization. This is another factor when controlling the manufacturing environment and is dependent on the concentration of the contaminants which is of critical importance as well as the motion (vector movement) of those contaminants. Studies have shown that when temperature differences occur, the contamination risk will increase with the increasing air flow through the chamber. There is a complex interaction of dispersion of contaminants, air movement and risk of airborne contamination that requires an understanding of the risk and evaluation of the lyophilizer during aseptic loading and unloading of the product [3].

Another strategy that some firms are taking is to design a risk evaluation that is quick and efficient while taking into account: what might go wrong, probability of it going wrong and the consequences (severity of risk). Systems have been designed based on starting materials used, containers used, complexity of sterilization and the aseptic procedure as well as the route of administration of the final finished product, possibility of post-contamination. This allows for the accurate reflection of the risk involved for each type of drug manufactured [4].

There is need a comprehensive in process sampling and testing plan to monitor and control the biological manufacturing process. When thinking about how microorganisms can enter the process it is prudent to consider the containers and samples themselves as well as personnel, environment and surfaces. Sample containers and samples themselves can lead to either false negatives or positives results. Containers should be both sterile and endotoxin free. The process of sampling and testing to monitor control of the manufacturing environment must be wide-ranging in nature to address both sterility and the presence of pyrogens [5-7].

## Conclusions

Microbial control of pharmaceutical manufacturing environments is a multifaceted and multifunctional task that is the responsibility of more than just those in Microbiology. It is important to have a solid conceptual understanding of the value of the science and the critical role Microbiology plays in the safe and effective use of pharmaceuticals. Microbial control should be built into the QMS of all manufacturing environments; from the design of the facilities to the quality of the water used to formulate to the containers used to fill. Though it is not representative to expect that a sterile environment will be at 0 CFU, which should not prevent industry from designing processes and controls towards that goal. The seriousness of microbial contamination in critical products cannot go understated and it is much less expensive to design a quality system with microbial control over your environment in mind, than it is to be in a 'reactive mode', constantly responding to out of spec (OOS) events that include failed batches, recalls and warning letters. It is the responsibility of both pharmaceutical manufacturers and the CMO/CDMOs that support them to collectively insure that the safest most effective product is on the market; a large part of this effort is achieved by ensuring that environment, process and product are free of microbial contamination.

## Disclosure

This paper was written by Dr. Law in her individual capacity. No official support or endorsement by Nitto Avecia Pharma Services is intended or should be inferred.

## Bibliography

1. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/ucm594437.htm#OMQ

2. Akers Michael J. "Basics of Sterile Compounding: Aseptic Processing". *International Journal of Pharmaceutical Compounding* 19.1 (2015): 49-56.

3. Ljungqvist B and Reinmüller B. "Loading and unloading of freeze-dryers: airborne contamination risks for aseptically manufactured sterile drug products". *PDA Journal of Pharmaceutical Science and Technology* 61.1 (2007): 44-50.

4. Ben-Horin SF and Rousso T. "Determination of Risk for Sterile Preparations". *International Journal of Pharmaceutical Compounding* 18.1 (2014): 30-34.

5. Bain D., *et al*. "Microbial Monitoring For Biological Drug Substance Manufacturing: An Industry Perspective". *PDA Journal of Pharmaceutical Science and Technology* 69.3 (2015): 451-460.

6. Hussong D. "Sterile Products: Advances and Challenges in Formulation, Manufacturing and Regulatory Aspects-A Regulatory Review Perspective". *AAPS PharmaSciTech* 11.3 (2010): 1482-1484.

7. Riley BS and Li X. "Quality by design and process analytical technology for sterile products--where are we now?". *AAPS Pharma SciTech* 12.1 (2011): 114-118.

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