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Commentary

Microbiological Monitoring of the Manufacturing Facility

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INTRODUCTION

At first it might seem that the direction for defining microbiological standards for non-sterile manufacturing environments to "scale down" those already defined for sterile manufacturing. However, this is not as easy as it would appear. Environmental microbiology standards for sterile manufacturing are mainly quantitative (colony forming unit cfu) (cfu per m^3, cfu per plate per 4hours, cfu per cm^2, etc.) and are limited to extremely low numbers, often zero (zero should defined as less than 1). The extremely highly specified environmental controls applied in sterile manufacturing make it possible to set and achieve the required limits. When environmental controls are less stringent (as in non-sterile manufacturing), the numbers of microorganisms not only increases, but also show more variability.

The consequences of the variability in numbers of microorganisms recovered from non-sterile manufacturing areas, and the relative weakness of the environmental control mechanisms, diminishes the effectiveness of quantitative standards. Limits are either set so high to accommodate the variability that they become meaningless, or set so strictly that they do not accommodate the intrinsic variability. They therefore result in frequent out-of-specification (OOS) conditions that cannot be sensibly rectified. In this latter case, the microbiological environmental monitoring programme most often falls into disrepute.

On the other hand, there are good arguments for setting limits for absence of the microorganisms, which indicate diminishing standards of hygiene, operator malpractice, system breakdown, etc. Gram-negative microorganisms are the greatest risk to liquids, ointments and semisolids. Although Gram-negative organisms are ubiquitous in nature in water and in drains, they are not all identically significant as potential contaminants of these preparations. Known Gram-negative pathogens should not be tolerated in manufacturing areas. However, there are other Gram-negative types, Ex: Enterobacter agglomerans, which need not always, be of great concern. The non-sterile environmental monitoring programme should balance the Types of Gram-negative organism (which may or may not be tolerable against the locations monitored) Type of product manufactured Severity of actionrequired when they are isolated.

Known Gram-negative pathogens are customarily addressed via attempted isolation of the indicator organisms, *Pseudomonas aeruginosa*, *E. coli* and *Salmonella*. Selective media are best used to ensure that these indicator organisms are not obscured by other, more resilient, microorganisms, which grow more rapidly and extensively on general media. The consequences of finding *Pseudomonas aeruginosa*, E. colior Salmonella or other pathogens while manufacturing or filling equipment are likely to be severe —batch rejection is a possibility, but this must be considered on a product-by-product, incident-by-incident basis. The consequences of finding them in a wash-bay, for instance, should not be as severe. Isolation of indicator organisms from these less critical areas should be seen as an early warning of a contamination source, which could lead eventually to manufacturing equipment or product contamination. Corrective and preventive actions (CAPA) against sources of contamination should be mandatory, and manufacturer may have to be suspended if the problems persist.

Gram-positive types may be similarly dealt with, concentrating on isolation of *Staphylococcus aureuson* suitable selective media. Someincidence of ubiquitous environmental Gram-positive types (such as *Bacillusspp* and *Micrococcusspp*) is inevitable, and unless excessive, should not give too much cause for concern. Gram-positive types should be considered of greatest significance in locations from which personnel are excluded and locations (ex: within filling cabinets) where personnel are expected to disinfect after rare and unusual intrusions. Isolation of Staphylococcus aureus in such locations, for example, means that something is not happening inthe manner intended.

All Gram-negative microorganisms should be restricted from manufacturing equipment, filling machines, etc. General media are best used for this purpose, on the other side the selective media used for the indicator organisms. The consequences offending nonpathogenic Gram-negative species on manufacturing and filling equipment, corrective and preventive action against the sources of contamination, but not necessarily action against product. As they may be indicative of the presence of pathogenic species at levels below the sensitivity of the detection methods used, manufacture may have to be suspended. It is to be expected that some Gram-negative microorganisms will be isolated from less critical areas, particularly those in which water is present. Unless isolates are of the indicator types or other confirmed pathogens, their importance should not be exaggerated.

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Actions and sanctions should be expected and applied when there are in fringments to microbiological limits applying to the manufacturing environment for liquids, ointments and semisolids. The most likely actions arising out from out-of-specification or atypical non-sterile environmental results are those relating to the control of the process, or relating to operators and facilities. The most frequently required actions are disinfection of an area or piece of equipment, or counselling to retrain personnel. These are typical corrective actions. Corrective actions are defined in terms of fixing the immediate problem. Additionally, attention must be given to preventive actions, for instance, replacing a defective item of equipment. Preventive actions are defined in terms of making sure the problem cannot arise again.

The most serious actions that can arise from an out-of specification result from microbiological environmental monitoring of non-sterile manufacturing areas are for product withdrawal (recall) or rejection. Neither action is likely to be required as a result of environmental data with no evidence of actual product contamination. Nonetheless it would be difficult to justify continuing manufacturing of, for example, a paediatric syrup in equipment from which *E. coli* or *Salmonella* is repeatedly isolated, or to manufacture an inhalation in equipment from which *Pseudomonascepacia* is isolated. Suspension of manufacturer is a viable and probable option pending thorough investigation, diagnosis of the root cause of the problem and implementation of adequate corrective and preventive action.

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