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A review on fungal contamination in pharmaceutical products and phenotypic identification of contaminants by conventional methods

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Microbial contamination of pharmaceutical products is one of the major reasons for product recall and manufacturing problems. Knowledge of the distribution of survival microorganisms

in pharmaceutical environments is critical in the process control of non-sterile and sterile pharmaceutical products. This knowledge is somewhat limited by the ubiquitous distribution of microorganisms in manufacturing facilities particularly fungal distribution. Identification of these fungi isolates from pharmaceutical environments using standard identification procedures requires experienced skilled technologists. To develop the proper corrective action when out of specification results are obtained, accurate fungal identification is needed if the contamination source has to be determined and tracked. Corrective action may not be effective if erroneous information is used to solve a given problem. This review provides guidance about knowledge of fungal contamination in pharmaceutical products and outlines an economic approach to phenotypic identification using conventional methods.

Key words: Fungal contamination, identification of fungi, staining methods, fungi in pharmaceutical environments.

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Review of oral insulin delivery systems

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To date, the only effective way of administering insulin has been by subcutaneous injections. The more convenient, less painful oral route would be ideal provided the obstacles to gastrointestinal absorption can be overcome. This article reviews research into delivering insulin safely and effectively by the oral route.

Key words: Diabetes, oral insulin, absorption enhancers, enzyme inhibitors, mucoadhesive polymers, particulate carriers, targeted delivery.

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A review of cleaning technologies for medical engineering: value added through high levels of cleanliness

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Selection of the most appropriate and effective cleaning technology makes an important contribution to quality and efficiency in the production of technical medical products. Not only can both be enhanced with modern cleaning technologies, they frequently make it possible to realise new product concepts as well.

Key words: Cleaning technologies, ultrasonic cleaning, medical engineering, supercritical carbon dioxide, plasma cleaning, surface cleaning.

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A comparative analysis of two different analysers used for determination of the Total Organic Carbon in pharmaceutical grade water

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Total Organic Carbon (TOC) is a routine test for pharmaceutical grade water. Several manufacturers supply equipment of different designs but there is a dearth of published, peer-reviewed, information evaluating the various analysers. In this study, we compared two TOC

analysers, both validated to the same pharmacopoeial criteria, but with different oxidation and detection methods. The results in this paper show that there were no unexplained out-of-specification results and that both analysers operated equivalently in terms of the pharmacopoeial 500ppb pass/fail limits. However, significant differences between the TOC levels reported from paired samples were observed: two paired samples recorded a pass/fail conflict (albeit flagged with an overestimation warning), as well as differences in analyser responses between spiked samples that contained low levels of nitro- and chloro-carbon compounds.

Key words: WFI, purified water, pH, nitrogen, halide, conductivity.

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Real-time microbiological air monitoring

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An innovative optical technology, aerosol cytometry, which enables real-time simultaneous detection and enumeration of non-viable particles and microorganisms has been tested. There is no requirement for laboratories, sample preparation or other materials. The purpose of these studies was to demonstrate the feasibility of this technology, as an alternative to conventional, growth-based methods for active air sampling. The studies were performed in grade C environments, both at rest and in activity, because they are controlled to a low level of microorganisms.

The results from three case studies are presented. The first study assesses side-by-side measurements using aerosol cytometry and conventional particle counters over 24 hours. In the second, data were collected during filling operations to investigate if microorganisms generated by human activity can be detected, and, in the third study, the effect of reducing airspeed velocity under a laminar airfow was investigated.

It was found that real-time active microbial air monitoring offers many opportunities for enhancement of environmental monitoring. However, more data need to be collected from different applications to understand the system capabilities, and the significance of using a time-base instead of a volume-base when interpreting microbiological data.

Key words: Microbiological air sampling, real time, aerosol cytometry, environmental monitoring.

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A comparative study of the two most frequently used methods in Sweden for collecting airborne viable particles is described. The measurements were performed in operating rooms during ongoing surgery. The results show that the two measuring methods, filter sampler and slit-to-agar sampler, give concentration values (CFU/m3) in the same range.

Key words: Microbiological air sampling, controlled environment, operating rooms, airborne contamination.

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Surface and air cleanliness in operating theatre environments

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In this paper, airborne particles and microbiological hygiene are reported from a hospital hygiene study. The surface hygiene was monitored on operating theatre equipment, instruments and other adjacent surfaces as well as protective clothing and shoes. The study was performed from June until December 2010 in four Finnish operating theatres. The information obtained will be used in the development of a comprehensive package for hygiene assessment in both operating theatres and other hospital environments.

Key words: Operating theatre hygiene, surface hygiene, hygiene survey, airborne particles, aerobic bacteria, yeast, mould, coliform, E. coli, S. aureus.

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Parenteral biologics delivery: recent progresses, key challenges and perspectives

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This review presents recent progresses in the field of parenteral protein delivery, with emphasis on the most successful technologies. Two strategies have been explored and developed to improve parenteral biologics delivery, providing long-acting protein formulations. One is based on post-translational modification/conjugation and, more recently, genetic fusion, to generate long-acting proteins with controlled molecular features and lower immunogenicity. A more recent strategy is conversely based on depot sustained-release formulations of unmodified proteins with specific functionality, such as release rate and pharmacokinetic profile. These new products bring significant improvements in convenience of administration, tolerability of treatment and compliance by reduction of injection frequency, as well as optimisation of safety/efficacy balance by modifying pharmacokinetics and achieving prolonged therapeutic concentrations. Advantages and limitations of both strategies and technologies are also discussed.

Key words: Parenteral biologics delivery, long-acting proteins, protein post-translational modifications, PEGylation, polysialic acid conjugation, fusion proteins, protein sustained-release formulations, gelling formulations, hydrogels, biodegradable polymer microparticles, nanoparticles, solvent-free protein formulation technologies, water-based protein formulation technologies, solid implants.

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Examination of air and surface particulate levels from cleanroom mats and polymeric flooring

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This paper describes a study undertaken in a biopharmaceutical manufacturing facility, which examined particle levels from the footwear of personnel entering a cleanroom and after stepping onto a cleanroom mat. The study compared six adhesive cleanroom mats and polymeric flooring and considered the change in the number of particles on footwear (uncovered shoes and shoes covered with an overshoe) before and after personnel had traversed cleanroom flooring. From this comparison, the level of reduction was greatest from the footwear of staff who had walked across the polymeric flooring. The study also

assessed the level of particles produced when the top layer of a cleanroom mat was removed, and these data are presented for information purposes.

Key words: Contamination control, cleanroom mat, polymeric flooring, cleanroom, particle counts.

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Science and Technology Feature

An improved leak integrity testing rationale for pharmaceutical and pharmacy isolators

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This technical review challenges the status quo for leak integrity testing of pharmaceutical (small scale) and pharmacy isolators, and proposes a new rationale. A single non-specific set of test values (from classification references like the ISO system) are insufficient; instead, both initial classification values and routine monitoring test values should be defined. On initial qualification, and at annual requalification, the more stringent classification criteria should be applied, but, during routine operation, a less demanding monitoring test level could be used to allow for inherent and, therefore, acceptable variability.

Key words: Isolator/glove leak integrity testing, pharmaceutical/pharmacy isolators.

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Investigating rapid microbial detection methods as an alternative to total aerobic microbial counts for non-sterile bioburden assessments

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Rapid microbial methods (RMM) have been shown to improve aseptic NHS quality assurance activities. This study investigates the potential to use these new rapid qualitative technologies for quantitative bioburden testing. The principle of dilution to extinction, extrapolation and an inference on original sample bioburden will be investigated. Non-sterile medicines manufactured within NHS Pharmacy are required to meet regulatory standards for microbial bioburden, which are currently measured by reference microbial methods (e.g. Total Aerobic Microbial Counts after 5 days incubation at 30°C). RMM can give results within 24 hours.

Initial studies will be required to determine equivalence or non-inferiority between the reference and alternative methods.

Key words: Microbial quality, pharmaceuticals, NHS, BacT/ALERT.

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Current thoughts on module-based GMP training

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After many decades of continuous growth, the pharmaceutical industry is facing a serious challenge: people and their competence will be the next driving force for the success of modern industry. To have a strong motivated, prepared and skilled workforce, a structured GMP training system needs to be established. A simple and self-consistent model of a GMP training system is presented, showing examples of GMP training modules, the tools to use them, evaluation of effectiveness and report of results to senior management. The model presented here has been shown to be appropriate in both customer and legal GMP inspections.

Key words: GMP, training, trainees, skills, motivation, module-based training programme.

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Study of proper placements of HEPA-filter units in order to prevent airborne contamination of autoclaves in aseptic production by using computational fluid dynamics

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Autoclaves are common process equipment used in the pharmaceutical industry. This type of process equipment can cause temperature differences relative to ambient air. During unloading autoclaves used for aseptic production, entrainment of room air into the loading chambers may occur creating contamination risks. To minimise these risks, high-efficiency particulate air (HEPA) filter units with unidirectional flow can be used to provide the chamber openings with clean air protection. This paper describes the use of computational fluid dynamics to simulate unloading of autoclaves used for aseptic production in try to improve the understanding of contamination risks of the autoclave chamber and present solutions of proper placement of HEPA filters in order to protect the openings of autoclaves.

Key words: Autoclave, aseptic unloading, temperature difference, airborne contamination, HEPA-filter units.

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