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Content and Abstracts

Viability of microorganisms in novel chemical and biopharmaceutical anticancer drug solutions

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Most anticancer drug products used in clinical practice lack antimicrobial properties. Therefore, materials and methods utilised to prepare the parenterally administered preparations must ensure sterility and avoid the introduction of contaminants and the growth of microorganisms. The aim of the study was to evaluate the growth potential of four different microorganisms in diluted ready-to-use novel chemical and biopharmaceutical anticancer drug preparations.
In three consecutive series, 14 different antineoplastic drugs were diluted to the lowest customary concentrations in polyolefin containers prefilled with 0.9% sodium chloride or 5% dextrose solution. Aliquots (9 mL) of each

anticancer drug solution were inoculated with 1 mL suspension of bacteria or fungi (Staphylococcus aureus, Enterococcus faecium, Pseudomonas aeruginosa and Candida albicans) to achieve approximately 104 microorganisms per mL. Pure vehicle solutions were used as positive controls in each series. The inoculated preparations were stored at room temperature (22°C) and protected from light. Samples (1 mL) were taken immediately and 1, 3, 5, 24, 48 and 144 hours after inoculation, processed and transferred to tryptic soy agar plates. The plates were incubated at 37°C and the colony-forming units counted after 24 hours.

The tested microorganisms remained viable in most of the anticancer drug solutions over a period of 144 hours after inoculation. Trabectedin was the only product generating distinct and rapid antibacterial activity. Viability of C.albicans was not affected by trabectedin, but growth of the fungus was retarded in temsirolimus-containing samples. Nab-paclitaxel suspension supported the growth of the selected bacteria and fungus.

Most of the novel anticancer drug products showed neither growth-retarding nor growth-supporting properties. Therefore, in pharmacy departments the anticancer drug products for parenteral administration should be prepared under strict aseptic conditions and refrigerated. Lack of antibacterial and antifungal properties should be considered when assigning extended expiry dates. Attention should be paid to the vulnerability of albumin-containing nab-paclitaxel suspensions to microorganism proliferation.

Key words: Biopharmaceutical anticancer drug solution, microorganisms, antimicrobial activity.
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Air filtration challenges and answers for dry heat sterilisation tunnels

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Dry heat sterilisation and depyrogenisation is considered to be one of the more critical process steps in medicine manufacturing, contributing to ensuring the sterility of pharmaceutical sterile (terminal sterilisation) and aseptic preparations. Inside such sterilisation and depyrogenisation tunnels, high-efficiency particulate air (HEPA) filtration plays an indispensable role in

protecting containers, such as vials or prefilled syringes, from contamination that might result in severe health risks for patients. Where the installed HEPA filter has to withstand frequent temperature cycles between ambient and up to 350˚C, operating conditions are challenging. To manage the challenges, and, therefore, not to adversely affect manufacturing throughput and product quality and safety, a careful selection of the high temperature HEPA filter is required. This paper describes the key challenges that have to be accommodated for dry heat sterilisation and depyrogenisation processes, and will present two selection criteria that have been found to be most important for a high temperature HEPA filter. The insights are based on extensive interviews that were conducted with both tunnel equipment manufacturers and pharmaceutical end users. Supported by various test cycles, through which air filter durability and particle shedding was defined, a new filter design will be presented that resolves well-known issues with the traditional high temperature HEPA filter design that has served the market for many years. The performance of the new filter design was proven by a field test in an existing dry heat sterilisation tunnel, of which the results will be presented. This paper will therewith provide new insights into how to mitigate process contamination risk by applying new, but proven, HEPA filtration technology. It will support the pharmaceutical industry to obtain a more stable and reliable dry heat sterilisation and depyrogenisation process.

Key words: Dry heat sterilisation, dry heat depyrogenisation, high temperature HEPA filtration, filter design, filter durability, particle shedding, filtration efficiency.

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Science and Technology Feature

Transfer of ready-to-use sterilised product primary packaging containers and single-use systems into small batch filling systems in isolators

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This article considers methods of transfer of ready-to-use sterilised product containers for aseptic filling in small batch isolators. Ready-to-use containers are typically in nests/tubs with protective packaging that requires removal on entry to filling isolators. Two types of transfer method are considered: type 1, with an automated outer packaging decontamination process just before entry into the filling isolator, e.g. electron beam, low pressure/temperature

plasma and hydrogen peroxide vapour; and type 2, mechanised de-bagging and no-touch transfer with a manual outer packaging disinfection step. The information provided aims to assist a risk-based selection process of the ready-to-use container transfer method.

Key words: Aseptic filling, small batch isolators, ready-to-use containers, no-touch transfer, ebeam, low pressure/temperature plasma, H202 vapour.
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Content and Abstracts

Settle plate exposure under unidirectional airflow and the effect of weight loss upon microbial growth

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Settle plates play an important part in the environmental monitoring programme and for the assessment of microbial settlement at key locations within cleanrooms, particularly when situated within unidirectional airflow devices. It is important that the exposure time of the settle plate is assessed to ensure that the proportion of weight loss (through the loss of moisture) does not result in a loss of growth-promoting properties. A second important concern is with avoiding cracks in the agar which might render reading sections of the exposed plate impossible. This paper outlines a case study to assess the exposure time through microbial growth promotion.

Key words: Environmental monitoring, cleanrooms, unidirectional airflow, settle plates, agar, microorganisms, microbial recovery.

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Assessment of degree of risk from sources of microbial contamination in cleanrooms; 1: Airborne

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The degree of risk from microbial contamination of manufactured products by sources of contamination in healthcare cleanrooms has been assessed in a series of three articles. This first article considers airborne sources, and a second article will consider surface contact and liquid sources. A final article will consider all sources and the application of the risk method to a variety of cleanroom designs and manufacturing methods.
The assessment of the degree of risk from airborne sources of microbial contamination has been carried out by calculating the number of microbes deposited from the air (NMDA) onto, or into, a product from various sources. A fundamental equation was used that utilises the following variables (risk factors): concentration of source microbes; surface area of product exposed to microbial deposition; ease of microbial dispersion, transmission and deposition from source to product; and time available for deposition. This approach gives an accurate risk assessment, although it is dependent on the quality of the input data. It is a particularly useful method as it calculates the likely rate of product microbial contamination from the various sources of airborne contamination.

Key words: Risk assessment, degree of risk, source, airborne contamination, micro-organisms, microbe carrying particles, MCP.

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Science and Technology Feature

Quality by design in an evolving manufacturing sector

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Regulatory guidelines are changing product quality focus from a reliance on end product testing to a quality-by-design (QbD) approach across the entire pharmaceutical product life cycle. The introduction of QbD elements to pharmaceutical manufacturing has the ability to speed up the time to market by facilitating scale-up during product development, enable real-time release and reduce the risk of batch failures. Pharmaceutical manufacturing approaches to make plants more efficient and flexible include a move towards continuous manufacturing platforms. As continuous manufacturing processes have no defined batch size, proving rigorous process control and fault detection is crucial to validate these processes. Continuous manufacturing, therefore, requires that a much greater burden is placed on tight process control. To achieve this level of control, in-depth material and process knowledge is required. QbD principles are, therefore, essential to ensure process control during continuous production.
This article introduces and discusses the regulatory principles of the QbD approach across the pharmaceutical product life cycle. It explores the role of QbD within an evolving pharmaceutical manufacturing sector. The implementation of QbD is discussed together with the concepts of quality target product profiles, material quality attributes, process parameter control, design space, process models and process analytical technology.

Key words: Quality by design, ICH Q8, ICH Q9, ICH Q10, real-time release, continuous manufacturing, batch manufacturing, critical material quality attributes, process models.

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Content and Abstracts

Validation of the Growth DirectTM system to perform pharmaceutical water bioburden analysis

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The validation of the Growth Direct system is described for the automated incubation and counting of microbial colonies on R2A media plates derived from a water bioburden test. The validation strategy and sample data are

given to demonstrate that the technology is accurate for enumerating microorganisms, accurate and precise for microbial recovery and equivalent to the current compendia test for water testing.

Key words: Rapid Micro Method, water validation, Growth Direct, TR33.

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Assessment of the disinfection of impaction air sampler heads using 70% IPA, as part of cleanroom environmental monitoring

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Active (volumetric) air-sampling is an important component of the environmental monitoring of cleanrooms. It is important that the results of such monitoring are accurate. One aspect of ensuring that the result is 'valid' is through minimising cross-contamination. The 'at risk' part of the sampler is the head. There are three alternatives to control cross-contamination during active air sampling contamination control: using multiple air samplers, autoclaving the sampler head in-between samples, or disinfecting the sampler head intermittently. This paper summarises a study where a disinfectant (70% isopropyl alcohol) was used to disinfect the head of an impaction air sampler between sampling sessions (spray-and-wipe technique). The study examined two factors: disinfectant decontamination effectiveness and the potential for the inhibition of microbial growth. With decontamination effectiveness, successive operations of an air sampler were examined within different cleanroom grades; with microbial growth inhibition studies, different disinfection time points were assessed. The paper concludes that this method of contamination control is effective and applicable to most cleanroom monitoring situations: it is unlikely to allow carry-over of microbial contamination and it is not shown to cause inhibition of microbial growth.

Key words: Environmental monitoring, active air sampling, biocontamination control, disinfection, cleaning, sanitisation, alcohol, culture media, microbiology.

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Science and Technology Feature

Requirements and environmental monitoring in pharmaceutical production versus operating rooms in hospitals with focus on airborne particles and microorganisms

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Clean areas used for aseptic manufacturing of sterile medicinal products are subject to governmental requirements and guidelines in order to minimise risks of particulate and microbiological contamination. High cleanliness is also a necessity in hospital environments to ensure safe conditions for the patients. The requirements for premises within the pharmaceutical industry are compared to those of the hospital, e.g. operating rooms including environmental monitoring with a focus on particle and microorganism levels.

Key words: Environmental monitoring, ultraclean air operating room, aseptic sterile production area.

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