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Content and Abstracts

Sampling plan for cleanroom classification with respect to airborne particles

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The concentration of airborne particles is a critical parameter for cleanrooms, clean zones and controlled areas. Particle concentration must be measured at representative locations for classification and monitored routinely or continuously at critical locations during operation.

Both ISO 14644-1:1999 and the new Draft International Standard (DIS) edition provide nine classes of cleanliness and specify both the number of sample locations for classification and the acceptance criterion for the data.
In the 1999 version of the Standard, the minimal number of sample locations is not based on statistical principles. The acceptance criterion is based on a statistical test, but only if the number of sample locations is less than 10. Thus, classification is based on statistical methods only for a small number of locations.
The revised ISO/DIS 14644-1 replaces this method with a statistical principle for selection of the sample locations. The acceptance criterion in the revised version eliminates the need for applying a statistical test to the data, and thereby simplifies the classification process.
The purpose of this paper is to present and discuss the new sampling plan for cleanroom classification and compare it with the previous approach in ISO 14644-1:1999. Section 2 of this paper presents and discusses the previous method, section 3 describes the new method in the ISO/DIS 14644-1 revision, and section 4 provides a discussion and conclusion.
All of the authors are members of ISO Technical Committee 209, Working Group 1; this paper was written on behalf of the entire Working Group.

Key words: Cleanroom, particle concentration, airborne particle, sample location, classification, statistical sampling.

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Design and characterisation of a novel environmentally responsive ophthalmic drug delivery system

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Pre-application, an environmentally responsive ophthalmic drug delivery system is in the liquid state and easily administered to the eye, whereas post-application, it is transformed into a highly viscous gel. The gel formed in vitro produced sustained drug release over an 8h period. From a gelation study, it was concluded that the gel can keep the formulation in contact with the cornea for longer and can allow the slow diffusion of drugs, which results in sustained release. This new formulation is a possible alternative to conventional eye drops due to its ability to enhance bioavailability through its sustained drug release and longer pre-corneal residence time. As the concept involved is novel and the methodology used for the preparation is as simple as that of conventional ophthalmic liquid dosage forms, it is industrially oriented and economical. In future, the developed system may help to improve patient compliance.

Key words: Sodium alginate, HPMC, sustained release, ion activated.

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Control of macroparticles in a clean manufacturing environment

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Macroparticles with an equivalent diameter greater than 5µm must be under control when products with a high visual quality are manufactured. Large size particles are also challenging for joint technologies where joint thickness is less than tens of microns. This paper presents control and measurement methods to assess risks that macroparticles can create in manufacturing.

Key words: Macroparticles, airborne particles, contamination.

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A study of a new type of swab for the environmental monitoring of isolators and cleanrooms (the heipha ICR-Swab)

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A study was undertaken to determine whether ICR-Swabs manufactured to heipha Dr. Müller GmbH were able to support the growth of a range of micro-organisms without demonstrating inhibition. The ICR-Swabs are designed for the purpose of assessing the microbial population on surfaces in EU GMP Grade A (ISO Class 5) clean areas or in isolators (or other clean air devices) for presence/absence testing. The ICR-Swabs were challenged with a selection of micro-organisms at both high and low populations in order to show that potential contamination could be detected. The study demonstrated that ICR-Swabs could recover each of the micro-organisms without any indication of inhibition.

Key words: Environmental monitoring, microbial counts, swabs, cleanrooms, contamination control, aseptic filling.

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Monitoring of air in clean environments – a comparative study with instantaneous microbial detection

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A comparison of data and experiences acquired from simultaneous measurements by a standard discrete particle counter, a standard slit-to-agar sampler and Instantaneuos Microbial Detection during evaluation of cleanroom clothing systems in a test chamber will be presented. Pros and cons of different techniques to be used in a low contaminated environment (EU Grade A) will be discussed.

Key words: Microbiological air sampling; environmental monitoring.

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Design and evaluation of gastro-retentive tablets of atenolol using HPMC polymer

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The present investigation concerns the development of gastro-retentive tablets of atenolol, which, after oral administration, are designed to prolong the gastric residence time and, thereby, increase drug bioavailability. Seven batches of tablets were made containing atenolol, polymers HPMC K4M, HPMC K15M and HPMC K100M, along with the gas generating agent, sodium bicarbonate.

The physicochemical properties of different formulations were evaluated for their buoyancy lag time, total floating time and swelling index. Tablets formulated using HPMC K4M and HPMC K15M combined with HPMC K100M (1:1), were hydrated faster, eroded faster and dissolved completely within 9hr, while tablets containing a different grade of HPMC remained intact and provided slow release for up to 8–9hr. It was evident from the study that the formulation F3 containing HPMC K100M (100mg) exhibited the shortest floating lag time of 50s, a total floating duration of more than 15hr and an in vitro drug release of 90.62% at the end of 9hr. The in vitro release data was treated statistically and it was concluded that atenolol released

from formulation F3 followed the Peppas model (r2=0.9988) with non-Fickian diffusion (n=0.761).

Key words: Atenolol, gastric residence, gas generation, HPMC K100M, swelling index.

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Stability of omeprazole oral preparations: effect of high gastric pH on the stability of the gastro-resistance coat

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Following reports of lack of efficacy for generic omeprazole tablets when switching between brands, an investigation was conducted into the stability of omeprazole at acidic pHs and on the effectiveness of the gastro-resistant coat of different brands of omeprazole capsules at the pH range of the stomach. The results indicate that, for the brand of omeprazole that was the subject of the defect report, the gastro-resistant coat could dissolute at pH 4.5 and this would

potentially lead to the release and subsequent degradation of the omeprazole active ingredient in the stomach. As a consequence, the gastro-resistant coat for this brand was reformulated and the defect problem resolved. The dissolution test in the British Pharmacopoeia monograph for omeprazole capsules and tablets has been amended to include a test at pH 4.5 and a market survey conducted to confirm that all brands of omeprazole tablets and capsules on the UK market complied with the test.

Key words: Omeprazole preparations, dissolution, degradation, gastro-resistant coating.

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GMPs for the 21st century and cleaning validation

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This paper describes the various methodologies involved in the implementation of new tools for cleaning validation. These methodologies are being developed to optimise the cleaning validation, and published experiences include the implementation of PAT (Process Analytical Technologies), QbD (ICH Q8), risk analysis (ICH Q9), ICH QIO, Six Sigma, Lean Manufacturing and the criteria of visually clean. In addition, new approaches are being used to establish acceptance limits for cleaning residues, which are based on the Threshold of Toxicological Concern (TTC). This approach is widely used by authorities that produce regulatory guidance and should allow limited safety data to determine an acceptable daily intake value based on known toxicological data of chemicals. The aim of this paper is to provide an updated view of the possibilities for working on the necessary improvement and optimisation of methods for cleaning validation in line with current methodologies being applied in so-called 21st century GMPs.

Key words: Cleaning, validation, QbD, risk analysis, PAT, TTC.

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Impregnation: a progressive method in the production of solid dosage forms with low content of poorly soluble drugs

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The production of poorly absorbable drugs with low content of active pharmaceutical ingredients is a contemporary trend in the pharmaceutical industry. The important problems associated with this topic are narrow content uniformity limits and low absorption in humans. Rapidity and simplicity of the production process are desired. This article describes

preparation of oral solid dosage forms by the method of "impregnation", which enhances bioavailability and improves content uniformity. Three examples demonstrating the preparation of tablets are listed here: (1) active substance is adsorbed onto the particles; (2) active substance permeates the porous structure of the particles; (3) active substance forms a solid solution on the surface of the particles. The particles are based on spray-dried lactose monohydrate, constituted by porous spherical particles. In all cases, the active substance is not absorbed easily and its content in the final dosage form is low.

Key words: Poor absorption, low content, content uniformity, bioavailability, spray-dried lactose, impregnation.

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Anti-falsification measures for packaging – repackaging or new packaging?

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Packaging is a key factor for consideration in measures to combat falsified medicines. Packaging that is still tamper-proof serves no further purpose once it is legally removed from the supply chain and replaced by new packaging. Packaging, repackaging and new packaging have been standard practices for parallel and repeat imports to date. Objections have, however, been raised and rightly so.

Key words: Falsified medicines, counterfeit, packaging, tamper proof, identification, authenticity, safety features, Directive 2011/62/EU

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Energy and environmental management in cleanrooms

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In order to maintain the environmental standards in pharmaceutical cleanrooms, as prescribed by regulatory authorities, the industry is, in the view of a number of authors, using excessive

amounts of energy. This, clearly, has significant cost and external environmental implications. This experiment was aimed at examining the potential reductions in energy usage and cost by making changes in the air supply to one cleanroom.

Key words: Cleanroom, particles, microbial, micro-organisms, clothing, air changes, change rate, activity, behaviour, settle plates, air sampler.

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Evaluation of two different types of contact plates for microbiological environmental monitoring

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Contact plates are used as part of environmental monitoring regimes for the microbiological assessment of surfaces in cleanrooms and other controlled areas. A range of different commercial suppliers of contact plates are available. These different types of plates vary in their ability to recover all cleanroom microflora and their counting efficiency. This paper presents an approach for selecting between contact plates produced by two of the different manufacturers of microbiological media for environmental monitoring (Redipor™ and 3P™) by examining the growth promoting properties and counting efficiencies of the two brands of contact plates.

Key words: Culture media, environmental monitoring, contact plate, RODAC, microbiological monitoring.

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Revision of ISO 14644-1:1999 – A progress report and explanation of some of the key issues and principles

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Report from ISO TC209 Working Group 02 Meeting 17th–18th October 2011 – ISO 14698-1 and -2

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Highlights

• Unanimous vote at Technical Committee (TC) 209 in support of Working Group (WG) 02's work to develop microbiological cleanliness classification schemes for controlled environments to allow classification of an environment by microbiological cleanliness levels alone (if appropriate).

• Draft International Standards Organisation (ISO) documents to capture current thinking expressed in new United States Pharmacopoeia (USP) <1116> chapter regarding incidence rates.

• Draft ISO documents to include concepts of 'normal and non-harmful' and 'objectionable' species as used in non-sterile areas.

• New Instantaneous Microbiological Device (IMD) technology to be explored.

• Draft ISO documents to include good manufacturing practice (GMP) for microbiological cleanliness.

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