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Content and Abstracts

Biological indicators don't lie, but in sporicidal gassing disinfection cycles do they sometimes confuse the truth?

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It is important to acknowledge the possible presence of “in-lot”, out-of-trend, highly resistant “rogue” biological indicators (BIs) in sporicidal gassing cycle qualification. Potential false-positive rogue results require management strategies. Equally, it is important to recognise when resultant BI positives are due to process lethality failure and not the BIs. *Geobacillus stearothermophilus* BIs are used in both steam sterilisation and hydrogen peroxide vapour disinfection cycle qualifications. The characteristics of BIs change to challenge the different processes of sterilisation and disinfection.

Information on BIs in the European¹ and United States Pharmacopoeia² relates primarily to BIs for sterilisation processes and the requirements do not fully translate for BIs used in disinfection sporicidal gassing cycles. As there are no specific references in standards or the Pharmacopoeias to sporicidal gassing as a surface disinfection process, a Parenteral Drug Association (PDA) task force is developing a technical report on “Biological Indicators for Sporicidal Vapor Phase Decontamination Processes: Specification, Manufacture, Control and Use”. This report will also make reference to hydrogen peroxide vapour as a surface disinfection process.

The presentation of the spore inocula has a significant impact on efficacy of the disinfection process to inactivate spores at a high level of reduction. Steam sterilisation, incorporating air removal and steam under pressure, has penetrative capability, hence spore clumps can be inactivated. In contrast, atmospheric applications with hydrogen peroxide vapour and other gaseous agents can be limited in penetrative capability, hence the main purpose of the process is surface disinfection/decontamination. This paper explains the science of the most commonly employed vapour phase disinfection process using hydrogen peroxide, and describes requirements for BIs to challenge the process. Strategies for managing unexpected BI positive growth as a result of “rogue” BIs are put forward.

Key words: Rogue biological indicators, hydrogen peroxide vapour decontamination

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The nature and the environmental impact of control of floor level contamination

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The nature of particulate contamination in the operation of cleanrooms is reviewed; particulate of greatest significance and most numerous is less than 10 microns and emanates primarily from movement of personnel. Significant contamination at floor level results from carryover of foot- and wheel-borne particulate and is normally controlled by the use of peel-off adhesive mats or, increasingly, by polymeric contamination-control flooring. Previously reported research on control of contamination is briefly reviewed to illustrate the distribution of particle sizes at floor level and the efficiency with which they are collected by peel-off mats and by proprietary contamination-control flooring. Polymeric flooring is shown to demonstrate significantly superior performance on particulate collection to peel-off mats for both viable and non-viable particulate and over a full range of particle sizes, especially on particulates less than 10 microns. Research undertaken over the past ten years has reported on studies related to footwear types commonly in use in cleanrooms and their influence on control of particulate contamination. Footwear with smooth soles releases particles most efficiently to the control surfaces of both peel-off mats and polymeric flooring; other soling types with ridged or patterned soles behave less predictably. Polymeric flooring demonstrates superior performance to peel-off mats for all soling types; the efficiency of peel-off mats is influenced adversely by some soling types in use, which can render peel-off mats almost totally ineffective. Comparative costs and ecological implications are reviewed by reference to an industrial case study. It is demonstrated that in a large installation requiring ten controlled entries, cost savings of as much as \$300,000 can be achieved over a two-year period by the use of polymeric flooring in place of peel-off mats; the installed area of the flooring is also 35 times greater than that of the ten mats combined, representing a substantially larger barrier of contamination. Over this period, the use of the recyclable flooring saves approximately 18 tonnes of raw material and

some 3-4 million MJ of energy used in the manufacture of the peel-off mats. Assuming that these are subsequently disposed of by incineration, the emission of greenhouse gases (CO₂) in manufacture and disposal is reduced by over 120 tonnes. A further consideration, with an environmental impact, is the disposal of the discarded peel-off mats. Most of these contain acrylic adhesives and polyethylene film. The cost of removal of the acrylic adhesives is substantial, and should be effected before disposal in landfill of the remainder of the used “peel-off” materials. Contamination peel-off mats from hospitals are required to be “de-contaminated” before being sent to landfill. Currently there is a requirement for a four log₁₀ reduction in microbial contamination before clinical waste can be consigned to landfill. This can lead to the risk of serious infection from waste thus disposed. Polymeric flooring, on the other hand, can be disinfected using antimicrobial disinfectants and therefore poses no health hazard to humans or the environment.

Key words: Cleanrooms, mats, polymeric flooring, particles, footwear, environmental impact.

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Comparing flow rates of microporous membranes

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Selection of membrane filters is complex and in instances confusing, particularly making fair comparisons between products and understanding certain performance claims. This paper identifies the issues and provides information about how to make good science-based comparisons and selection decisions, especially concerning flow rate.

In some instances claims have been made to declare similarity between flow rates through 0.1-micron and 0.2-micron-rated filters; these claims do not fit with criteria defined by certain principles of physics, for example the Hagen–Poiseuille law. Furthermore, 47mm discs have been used to compare flow rate performance of filters of the same pore size, instead of the actual device used in the filtration process, for example 10-inch elements. Performance claims and flawed test methods require elaboration and clarification. This paper discusses in detail the factors influencing flow, as well as the appropriate test to compare flow performances of different filters.

Key words: Flow rate, porosity, effective filtration area, filter design, filter membrane, pore size rating, process parameters.

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GMP – origins to today: some personal reflections

John Sharp

The following is an edited transcript of a paper presented at the Annual Conference of The Pharmaceutical and Healthcare Sciences Society on 16 October 2008. In order to preserve something of the flavour of the author's presentation, much of his personal style has been retained.

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Developments in the packaging of pre-filled syringes

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The pre-filled syringe is an increasingly attractive presentation for both new and established parenteral pharmaceuticals and vaccines. In this article, the author explores how innovative carton packaging solutions can enhance this presentation whilst meeting the stringent requirements of both product protection and environmental sustainability. He analyses recent developments in the packaging of pre-filled syringes for pharmaceutical products and considers trends for the future.

Key words: Pharmaceutical packaging, carton packaging for pre-filled syringes, top-load carton, tamper-evident packaging for pre-filled syringes, packaging machine for top-load cartons, sustainability

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Applications of nanoparticle tracking analysis in nanoparticle research – a mini-review

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Nanoparticle tracking analysis (NTA) is a new technique for the rapid, direct and real-time visualisation of nanoparticles in a liquid. Based on a laser-illuminated optical microscope, nanoparticles are seen as light-scattering centres moving under Brownian motion. A video of the movement of each particle is analysed on a frame-by-frame basis and the particle's size is established from an analysis of the average speed of movement. Because each particle is measured separately, it is possible to measure particle size and relative light-scattering intensity at the same time, allowing better resolution of mixtures of different particle sizes or types within a sample than would be possible with conventional dynamic light-scattering techniques such as photon correlation spectroscopy. Importantly, particle count or concentration can be recovered. This review summarises the applications and sample types to which NTA has been applied to date.

Key words: Nanoparticle analysis, size distribution, Brownian motion.

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Compatibility and stability of polygeline (Haemaccel) with different brands of cefotaxime

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Compatibility of the polygeline-based blood plasma expander Haemaccel with cefotaxime sodium was examined in the context of its potential use in circulatory insufficiency, in threatened and established shock, because drug stability and compatibility are critical elements in the accurate and appropriate delivery of drug therapy to patients. Treatment, safety, acceptability and efficacy may be affected by drug instability or incompatibility. This study was initiated to specifically and critically assess the compatibility of Haemaccel with cefotaxime sodium with the aim of delivering safe, appropriate, acceptable and efficacious administration of two different drug products simultaneously in emergency situations.

Key words: Cefotaxime, Haemaccel, compatibility, acceptability.

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Formulation and evaluation of rapid-dissolving tablet of poorly soluble drug domperidone

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The purpose of this study was to develop novel cyclodextrin-containing tablet formulations of domperidone. Complexation of domperidone with methylated- β -cyclodextrin (M- β -CD) was studied by the phase-solubility method. The aqueous solubility of domperidone increased as a function of cyclodextrin concentration, showing an AL type phase-solubility curve. A solid domperidone/M- β -CD complex was prepared by ultrasonification. To confirm complex formation, the complex was characterised by Fourier transform infrared (FTIR) spectroscopy, powder X-ray diffraction and differential scanning calorimetry techniques. FTIR studies showed that the drug was intact in the complex, whereas powder diffraction studies showed that the M- β -CD complex was amorphous. Solubility studies showed complexation increased domperidone solubility as compared to pure drug in 0.1M hydrochloric acid and distilled water. Analysis of drug content confirmed that ultrasonification is an efficient method to prepare inclusion complexes.

After characterisation of inclusion complex, tablets were prepared using different combinations of superdisintegrant, sodium starch glycolate and crosspovidone. All the formulations showed more than 90% release of domperidone. Batch FP6 showed the most rapid release of domperidone (99.95% within 25 min), whereas the marketed formulation showed 43.5% release in the same time. The results show that rapidly dissolving tablets can be prepared using M- β -CD, but the combination of superdisintegrant does not have a significant effect.

Key words: Cyclodextrin complexation, ultrasonification, domperidone, superdisintegrants, rapidly dissolving tablets.

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Quality assurance issues within the temperature- controlled supply chain – a contract manufacturer’s perspective

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This article provides a contract manufacturer’s perspective on quality assurance issues with respect to both starting materials and medicinal drugs that have to be handled under controlled temperature conditions. Based on the good practice requirements for storage, distribution and transport, key elements to be considered in the pharmaceutical quality assurance management systems and thus written documentation (standard operating procedures) are defined. Additionally, experiences from daily life as a contract manufacturer may provide valuable

information for quality assurance systems to be established at the contractor's and the manufacturer's site.

Key words: Quality assurance, supply chain, good storage practice, good distribution practice, good transport practice

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Proposed strategy for high containment of manufacturing machines used for highly hazardous products

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This work describes a strategy for implementing a system on existing manufacturing machines to provide a high-containment environment. This enables these machines to be used in GMP high-containment facilities, allowing the production of highly hazardous pharmaceutical products such as cytotoxics and cytostatics.

The market in highly hazardous pharmaceutical products has been developing over the past 5 years and is expected to increase exponentially in the next few years. The concept of high-containment facilities and machines is therefore of interest to companies that make such products or plan to do so in the future.

It is recommended that the proposed system be implemented in parallel with the design of high-containment facilities. This work is described in a sequential manner, starting with the design, implementation and qualification of the proposed containment system.

Based on the results obtained, it is concluded that the flexible isolator system could be used as a containment barrier, offering an alternative when high-containment machines are required in pharmaceutical manufacturing. Personnel using this system should wear appropriate personal protective equipment. The system is easy to implement and represents a less costly way of conducting pharmaceutical operations in a GxP high-containment environment.

Key words: HSE regulations, highly toxic products, high containment, manufacturing machines.

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Systems for sustained ocular drug delivery: a review of stimuli-sensitive in situ gel-forming systems

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Formulation development for ophthalmic drug delivery is one of the most challenging fields for investigators due to various limitations enforced by the eye. It includes factors such as specific features of the eye, the accuracy of the dose to be administered and the tear turnover rate affecting drug residence time, which causes different patterns of absorption. The conventional formulations such as solutions, suspensions and ointments show some constraints such as increased precorneal elimination, high variability in efficiency affecting bioavailability of drug and blurred vision due to the bases of the ointment formulations. In situ stimuli-activated gel-forming systems are liquid upon instillation and undergo phase transition in the ocular cul de sac to form a visco-elastic gel as a response to environmental changes such as temperature, pH or ionic strength. In the past few years, a number of new temperature-, pH- and ion-induced in situ gel-forming systems have been reported for sustained ophthalmic drug delivery. This review includes a description of various stimuli, associated with the ocular environment, which are proposed for use on such polymeric systems to achieve prolonged contact time of drugs with the cornea and to increase drug bioavailability.

Key words: Ocular drug delivery, in situ gel system, pH stimulated, temperature stimulated, osmotically stimulated, tear turnover.

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Chitosan-coated mucoadhesive multiparticulate drug delivery system for gliclazide: in vivo–in vitro correlation

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The purpose of this research was to develop optimised mucoadhesive microcapsules of the antidiabetic drug gliclazide and systematically evaluate their performance. Alginate microcapsules coated with the mucoadhesive polymer chitosan were prepared by an ionotropic gelation technique utilising calcium chloride (CaCl₂) as a cross-linking agent, to take advantage of the swelling and mucoadhesive properties of alginate beads for improving the oral delivery of gliclazide. The encapsulation efficiency and release rate of drug from microcapsules varied according to the concentration of alginate, the percentage of cross-linking agent, time of curing and particle size. The microcapsules obtained were discrete, spherical and free flowing. The chitosan-coated microcapsules exhibited good mucoadhesive properties in the in vitro wash-off test and also showed a high percentage of drug encapsulation efficiency. Swelling behaviour was strongly dependent upon the chitosan and alginate concentration. The in vitro release study indicated that the swelling was the main parameter in controlling the release rate from microcapsules. In vivo studies on diabetic rabbits demonstrated a significant hypoglycaemic effect when compared with marketed gliclazide (80mg) tablets. The results showed more than 30% reduction in blood glucose level up to 12 hours following administration.

Key words: Mucoadhesive microcapsules, gliclazide, encapsulation efficiency.

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Contamination risks due to door openings in operating rooms

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In view of the ongoing discussions concerning the need for guidelines and contamination control in operating rooms, dispersion of airborne contaminants through door openings is discussed in this paper.

Some mathematical models are described. The increase of the concentration of viable particles is predicted. The results show the importance of air cleanliness outside the operating room door in connecting areas/rooms when operations susceptible to infections are performed.

Key words: Contamination risks, door openings, hospital infections, operating rooms

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How instantaneous microbial detection can be used by pharmaceutical manufacturers

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This article discusses an optical instrument for instantaneous detection of microbes in the environment. The Instantaneous Microbial Detection instrument, IMD, has the capability of detecting the presence of bacteria and fungi in the environmental air. Its intended application is for environmental monitoring in a pharmaceutical facility.

The IMD instrument uses elastic light scattering (Mie scattering: an optical phenomenon where the size of the scattering particle is comparable to the wavelength of light. The intensity of Mie scattering is dependent on the size of the particle—a useful means for size measurement) to measure the particle size, and inelastic scattering (intrinsic fluorescence) from metabolites inside microbes to differentiate microbes from inert particles. Since the metabolites (e.g. NADH and riboflavin) and other proteins necessary for the generation of this intrinsic fluorescence are present within the cells of microbes, this technique has a broad microbial detection range without the need for sample preparation. The efficacy of the IMD instrument in detecting microbes was verified by a series of aerosolized bacteria tests comparing IMD with standard microbial culturing methods.

The IMD can be used to detect microbes in the environment in real time and on a continuous basis. We will discuss the potential applications of this technique in pharmaceutical aseptic operations. Test data of the IMD will be presented.

Key words: Microbial detection, environmental monitoring, real time, aseptic, fluorescence, optics

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Moving toward 100% raw material inspection with a handheld Raman spectrometer

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Pharmaceutical manufacturers are under pressure to minimize the current costs of incoming raw material inspection as well as increase their testing capacity to accommodate expanded production volume and more stringent regulatory requirements. Current spectroscopic techniques for raw material inspection are described and compared. A handheld Raman spectrometer, suitable for use by non-technical personnel, was shown to be an attractive option for identity testing of most raw materials used by pharmaceutical manufacturing facilities.

Key words: Raman spectroscopy, material verification, raw material identification, incoming inspection, handheld spectrometer, portable Raman.

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Antimicrobial preservative use in parenteral products: An overview

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Antimicrobial preservatives are compounds that are commonly added to multi-dose formulations. These preservatives prevent the growth of microorganisms in the event that they become inadvertently introduced during removal of doses from the container. This article summarizes the most commonly used antimicrobial preservatives in parenteral products and the regulatory requirements that must be met to demonstrate their effectiveness. Excluded in this review are generic parenteral drugs that contain antimicrobial preservatives and lyophilized products that are reconstituted with diluent containing these preservatives.

Key words: antimicrobial, preservative, parenteral, phenol, m-cresol, benzyl alcohol.

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