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Content and Abstracts

Disposables – breathing new life into existing facilities – a case study

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The biotech industry has matured and facilities now have to be able to adapt quickly to new regulatory expectations and new processes. This is a case study showing how the use of disposable technology can help in this goal without the need for major capital investment.

Key words: Disposables, case study, new regulations, adapt

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Wireless particle monitoring of pharmaceutical cleanrooms

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The pace of development within the wireless community is getting faster and faster every day. This enables us to communicate with the world and receive information in totally new ways. However, the pharmaceutical industry is not always picking up new technology and show the tendency to stick to the old techniques, which by nature of the business they are in, they are somewhat forced to do since the cost of errors can be fatal. This article will explain how the new wireless technology can improve the way that particles are monitored within the pharmaceutical clean rooms where aseptic manufacturing is taking place.

Key words: Wireless, particle monitoring, particle sensor, cleanroom.

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Examination of the potential for carbon dioxide gas ingress into pharmaceuticals during dry ice distribution

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To ensure patient safety, a clinical trial pharmaceutical product must be as equally fit for purpose on arrival at a clinical centre as it was when released by the manufacturer's Qualified Person. Therefore, any transit arrangements connecting the clinical centre with the supplier must be carefully considered and appropriately controlled, especially where shipment is to be made in the cold or frozen temperature range. Regulatory interest in this area of pharmaceutical operations is high, and may constitute a portion of an Investigational Medicinal Products Manufacturing Authorisation licence inspection.

An inspector's enquiry as to the potential for a dry ice gaseous atmosphere to cause product spoilage through carbon dioxide gas ingress into vials was investigated. Under laboratory conditions, and using passive gas monitoring as well as a traditional bench chemistry indicator, carbon dioxide was not detected at any higher than background atmospheric levels in sealed vial containers subjected to mock dry ice transit conditions. The risk of product spoilage by such a route would therefore not be expected to be a significant product quality risk.

Key words: Phase I, carbon dioxide, distribution.

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Intravenous ibuprofen lipid emulsions – formulation and in vitro evaluation

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A method has been developed to produce stable lipid-based carrier system for parenteral use as a drug carrier. Soybean oil emulsions of ibuprofen were prepared using a mixture of lecithin and non-ionic surfactants. Lecithin alone was found to possess poor emulsifying properties, hence the effects of Tween 20, Tween 60, Tween 80, Brij 35 and Pluronic F-127 were determined on the basic system of soybean oil:lecithin (1:0.12) in order to facilitate the emulsification process. Tween 80 and Pluronic F-127 were proved to possess favourable properties as co-emulsifiers in combination with lecithin with slightly more preference for Tween 80. Emulsions prepared using both the co-emulsifiers in the basic system exhibited a mean droplet size in the range of 40-50 nm (polydispersity <1) and was not altered markedly with time up to 7 days. Surface charge was found to be in the range of -45 to -50 mV indicating the presence of anionic components in lecithin. Electrical conductivity was increased from 17.5 to 18.4 mS/cm with time, confirming the decrease of pH from 8.0 to 7.41. Drug content of the emulsion was found within the pharmacopoeial limit. In vitro release studies showed 70-80% release of ibuprofen content from the emulsion within 24 hrs by dialysis sac technique, revealing that the release of drug was probably controlled by oil-water partition rate of emulsion under perfect sink conditions. The release profile was found to be best fitted to zero order kinetics. The stability of the emulsion was very good (>6 months) at 0°C, 25°C and 40°C. It was deduced from the overall results that Tween 80 and even Pluronic F-127 served as a better co-emulsifier in the basic system of soybean oil and lecithin. On the basis of the above results the emulsion is suitable for parenteral administration and has potential as targetable carrier for site-specific drug delivery.

Key words: Lipid emulsion, liposphere, ibuprofen, emulsion stability, phospholipid.

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Annex 1 of the EC Guide to Good Manufacturing Practice (EC GGMP) and continuous particle monitoring – help or hindrance for cleanroom manufacturing?

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Point-of-use continuous particle monitoring systems have directly replaced manifold-based (non continuous) systems within our pharmaceutical cleanroom manufacturing areas. A review of comparative data shows that the point-of-use system has a greatly increased particle collection capability compared to the manifold system. This has been demonstrated to be beneficial within the EC Grade A areas but less useful in EC Grade B1 areas. Monitoring for larger particles (≥5µm) to comply with the requirements of Annex 1 of the EC GGMPs1 has been shown to present a number of practical issues. However, adequate and more appropriate

particle monitoring can be achieved by recording particles at the smaller (≥0.5µm) particle size only.

Key words: Particles, continuous monitoring, point-of-use, cleanroom

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Particle and microbial airborne dispersion from people

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The airborne dispersion of particles from 55 people (30 females and 25 males) was measured. The dispersion per minute of microbe carrying particles (MCPs) averaged 2,400 when wearing personal indoor clothing, and 177 when wearing cleanroom garments. One exceptional person, whose dispersal rates were not included in these results, dispersed 11,000 per minute when wearing cleanroom garments. The dispersion rate of particles ≥5µm per minute averaged 332,000 when wearing indoor clothing, and 37,300 when wearing cleanroom garments. The dispersion rate of particles ≥0.5µm per minute averaged 2,130,000 when wearing indoor clothing, and 1,020,000 when wearing cleanroom garments. The dispersion rates for particles and MCPs were higher in males than females. Depending on the method used, the average equivalent particle diameter of the MCPs was 9µm or 18µm.

There was no situation where the dispersion of MCPs was not accompanied by substantial numbers of both ≥0.5µm and ≥5.0µm airborne particles, and there appears to be little advantage in measuring particles ≥5.0µm when using airborne particle counting to indirectly monitor the dispersion of MCPs. When wearing cleanroom garments, the ratio of ≥0.5µm particles to MCPs was found to average 5,800:1, and for ≥5.0µm particles it was 210:1.

Key words: Particle; microbial, airborne, dispersion, people.

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Quantitative risk modeling assists parenteral batch disposition

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Quantitative Risk Modeling and Simulation (QRMS) is a well recognised and sophisticated automated modeling technology with, as yet, an unrealised potential for application in aseptic manufacture. In contrast to contemporary risk assessment tools and techniques QRMS is rapid, generating objective assessments of risk by simultaneously evaluating the interaction of large numbers of risk factors and accounting for the uncertainty of data. Currently the batch disposition of aseptically manufactured parenteral product presentations is partly accomplished by the informed evaluation of all controls and circumstances associated with aseptic manufacture including, but not limited to, consideration of environmental, personnel bioburden levels and aseptic interventions. A significant portion of the batch disposition process is therefore an assessment of the risk of bioburden ingress during aseptic manufacture. Here a case study is presented illustrating the utility of QRMS to swiftly, rigorously and consistently compare the bioburden ingress risks associated with an aseptically manufactured lot and its equivalent process simulation. This comparative evaluation permits a rigorous appraisal of product quality directly interpretable as a sterility assurance level. QRMS therefore represents a potential tool assisting the expedient assessment of batch quality aiding lot release to make for an efficient and exacting batch disposition process.

Key words: Risk assessment, aseptic manufacture, risk modeling, lot release, batch disposition.

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Contribution to the automation of the USP- II dissolution test

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This work establishes solid bases for the automation of the analytical technique: "dissolution test USP-II". Included is an analysis of the strong and weak points of the method, as well as the internal and external parameters of the equipment. The analysis of these factors was performed in order to validate the transference of manual analytical methods to automated methods, demonstrating the reliability and equivalence between them. This transference of methods should reduce the lead time in the analysis of products and therefore increase the productivity in the laboratory.

Key words: Automation, dissolution test, USP-II, comparative validation.

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The current and future regulatory position with respect to pharmaceutical starting materials

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The current and future requirements for GMP for starting materials used in the manufacture of medicinal products marketed in the EU places new responsibilities on starting materials manufacturers, finished product manufacturers and European regulators. These new responsibilities are designed to improve the safeguards in the manufacture of medicinal products by tightening controls at all points in the supply chain from manufacture of the starting material through to its final incorporation into the finished medicinal product that will be supplied to the patient.

Although any point of this chain may be inspected by European inspectors, the primary responsibility for supervision is given to the site responsible for EU release of finished product batches. A number of provisions to implement the improvements in communication between

regulators will be assured through the new EudraGMP database, which will also provide an opportunity to be more transparent on inspection outcomes.

Key words: Good Manufacturing Practice (GMP), active substance, excipient, authorities, responsibility, supplier

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Greener cleanrooms

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Cleanrooms continue to waste energy despite evidence that considerable savings can readily be made by simple solutions, which will also have the effect of reducing the burden on the environment.

Key words: Cleanrooms, environment, environmental burden, energy reduction.

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The quality of starting materials – sampling

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The implementation of GMP requirements for the manufacture of Active Pharmaceutical Ingredients (APIs) and the implications for pharmaceutical manufacturers are considered. Problems of sampling of deliveries of starting materials are discussed.

Key words: Starting materials, APIs, GMP, ICH Q7A, auditing, guides/regulations, samples, statistics, representative samples

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Preparation of ophthalmic insert of acyclovir using ethylcellulose rate-controlling membrane

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The aim of the present investigation was to prepare controlled release ocular inserts of a polar drug, acyclovir, for continuous delivery to the eyes for 5 days. Reservoir type ocular inserts, comprising a reservoir film of sodium alginate and rate-controlling membrane of ethylcellulose in different concentrations, were prepared by film-casting technique on Teflon-coated petri dishes and tested for drug content, physical characteristics, interaction between drug and polymers due to sterilization by gamma radiations and in vitro drug release. All formulations contained 2mg acyclovir. Reservoir film containing 2.5% sodium alginate and 48% PEG 400 by weight of polymer as plasticizer was considered best for the formulation of the ocular insert because of its maximum folding endurance (20 ± 2) and percentage elongation at break (18 ± 0.57). On the basis of in vitro drug release studies, the formulation containing 2% ethylcellulose was found to be better than other formulations, with 91% drug release in 120 hr. It was therefore selected and subjected to in vivo and stability studies. A high in vitro-in vivo release correlation (0.989) was observed for the formulation. The concentration of acyclovir in aqueous humour reached above the reported Css of 1.7µg/ml after 8hr and remained almost constant up to 5 days; however acyclovir concentration could not be detected after 4hr on administration of 3% ophthalmic ointment. Ocular inserts were found to be stable with no interaction due to sterilization by gamma radiation. Thus, ocular inserts conclusively demonstrated controlled release of acyclovir with a constant concentration in the aqueous humour for 5 days.

Key words: Ocular insert, acyclovir, aqueous humour, sodium alginate, ethylcellulose, ophthalmic insert.

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Regulatory consequences of implementing rapid microbiological methods

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The European Pharmacopoeia has recently published a chapter, whose objective is to facilitate the implementation and use of RMMs.
A change to RMMs generally requires a variation to the MA but this may be unnecessary in the case of standard water if the change is site specific.

Key words: Rapid microbiological methods, pharmacopoeia, water, PAT, variations.

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Content and Abstracts

Flow microscopy for particulate analysis in parenteral and pharmaceutical fluids

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The application of a new direct flow-microscopy technology to the analysis of suspended particulates in parenteral fluids is described. Digital images of individual particles in a flowing sample stream are captured in real time and analysed by the system software. In addition to the direct visual insight into the nature of the particle population, automated shape analysis allows specific sub-populations such as aggregates, contaminants, bubbles or silicone droplets to be quantified. The technique is highly sensitive and, for protein formulations, measured concentrations are often one or more orders of magnitude higher than those found in the same sample using standard methods. Accurate concentrations may also be measured, even for samples having only a few particles per ml. Unlike light obscuration and scattering techniques, results do not depend on the particle shape or material type.

Key words: Flow microscopy, particle, parenteral, protein aggregation, image analysis

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Microbiological contamination of eyedrops. Part 1: Review of the literature

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Commercial, topical, ophthalmic products ("eyedrops") are prepared and manufactured under accepted pharmaceutical standards in plastic, squeezable, unit-dose or multiple-dose containers. Eyedrops are delivered to the consumer as sterile, sealed products guaranteed to be sterile until the container is opened and used. Often, multiple-dose eyedrops contain antimicrobial preservatives to minimise contamination of the product during use. Standard in vitro efficacy tests measure the activity of these antimicrobial preservative systems in eyedrops. In these tests, fairly high, unrealistic, levels of micro-organisms are used to challenge the product. Even this antimicrobial preservative barrier system does not necessarily prevent microbial contamination when these products are misused after opening by patients or practitioners. Patient compliance to good practices of administration of their eyedrops undoubtedly provides the most important element in protecting eyedrops from contamination. Extensive review of the literature spanning three decades indicates that approximately 9.1% of used ophthalmic products become contaminated during use. Conversely, 90% of eyedrops do not. Few of the literature studies were quantitative and most relied only on the detection of micro-organisms in used samples of eyedrops. Over the three decades of reports included in this survey, there were very few cases of grossly contaminated eyedrops that caused ocular infections. This fact tends to indicate that the current level of eyedrop contamination in the field is tolerable and not a major health hazard.

Key words: Microbiological contamination, eyedrops, in-use testing, preservatives.

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Installation of a new Highly Purified Water plant during on-going company operations

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This article describes how hameln pharmaceuticals implemented a new pharmaceutical water treatment facility without significantly disrupting current production. Purified water is the

primary raw material for a company specialising in the manufacture of preparations for parenteral use, so it was essential to minimise the time during which the water was unavailable.

In diesem Beitrag wird beschrieben, wie das Pharmaunternehmen hameln pharmaceuticals gmbh eine neue Pharmawasseraufbereitungsanlage nach umfangreicher Qualifizierung (DQ, IQ, OQ) in Betrieb genommen hat, ohne dabei die laufende Produktion in größerem Umfang zu stören.

In drei Phasen verläuft parallel zur Montage und ständigen Kontrolle der Betriebsparameter die Qualifizierung und Validierung der Anlage sowie des Aufbereitungsprozesses. Dabei wird vor allem auf eine ausführliche chemische und mikrobiologische Analyse Wert gelegt, um den Qualitäts-an-forderungen der Arzneibücher zu genügen.

Erst wenn alle Akzeptanzkriterien der Validierungsanweisung erfüllt werden und die Wasserauf-bereitungsanlage somit in der Lage ist, dauerhaft und reproduzierbar HPW zu erzeugen, ist die Qualifizierung erfolgreich abgeschlossen.

Key words: Highly Purified Water, water treatment plant, reverse osmosis, electro-deionisation, ultrafiltration, installation.

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Check list for the evaluation of insulation containers

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Insulation containers are used for the shipment of pharmaceutical preparations, perishables and temperature-sensitive cargo under cold chain conditions. The boxes differ widely in their construction, performance and ability to maintain the cold chain for a predetermined period of time. The check list described here helps to evaluate and compare the insulation containers. This article focuses on the pharmaceutical sector and passive systems (ie no external energy is needed to maintain the cold chain – the box is conditioned with cooling elements).

Key words: Cold chain, insulation containers, passive cooling, validation, usable net volume.

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A new standard for benchtop sterilizers

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The history and role of an Authorised Person (Sterilizers) and the introduction of a European standard for small steam sterilizers are discussed.

Key words: Authorised Person (Sterilizers), benchtop sterilizer, portable sterilizer, decontamination.

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