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Content and Abstracts

Microbiological contamination of eyedrops. Part 2: Evaluation of proper and improper administration

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Commercial eyedrops may become contaminated with micro-organisms during patient, practitioner or clinic use. Manufacturers and practitioners routinely warn the user never to touch the tip of the eyedrop dispenser to any surface while administering the eyedrops. This article presents results from studies designed to evaluate the level of contamination that can occur inside eyedrop containers after appropriate and inappropriate use of the dispensers. This investigation represents a novel approach to the traditional microbial challenge tests to determine the robustness of preservative systems of multidose eyedrops in the real world. A vulnerable, non-preserved saline solution with no added preservatives was chosen as the test formulation to represent a "worst-case" scenario and help estimate the level of antimicrobial preservative needed to protect these products. This approach considers single and multiple administration of a non-preserved test formulation, ie non-preserved saline. Two studies using human volunteers showed that touching the eyedrop dispenser to the conjunctiva, cheek or

hand, one or more times, increased the contamination rate over proper administration (ie without touching the dispenser tip to any surface). Not surprisingly, the levels of contamination were the greatest when the facial cheek was touched multiple times over a 5-day period during administration. The studies were quantitative and found these levels ranged from 0 to 10,000 colony-forming-units (CFU) per eyedrop dispenser. Nevertheless, in general, most of the data indicate that very few organisms contaminated the non-preserved saline used in these studies. The conclusion is that this challenge approach is a reasonable way of assessing microbial contamination of multiple-dose products. Also, the levels of contamination required by the compendial preservative efficacy tests seem to be inordinately high and unrealistic in light of these data from this model.

Key words: Microbiological contamination, eyedrops, eyedrop dispensers, testing, appropriate or inappropriate administration, preservatives

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Achieving technology transfer of biopharmaceuticals from research to aseptic processing in cleanrooms for clinical trials

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The adoption of the European Union (EU) Clinical Trials Directive has meant that academic research workers who wish to move research products into Phase I clinical trials must have the investigational medicinal products (IMPs) manufactured to meet the requirements of EU good manufacturing practice (GMP). This article discusses some of the issues facing the manufacturer of biopharmaceutical IMPs when transferring the production processes for recombinant proteins or plasmid DNA from the research bench into a GMP facility.

Key words: Biopharmaceuticals, investigational medicinal products, clinical trials, aseptic processing, cell banks.

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Comparison of dry-heat depyrogenation using three different types of Gram-negative bacterial endotoxin

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The aim of this research was to compare the destruction of the standard Escherichia coli endotoxin used for the qualification of depyrogenation processes, as recommended by the USP, with the destruction of endotoxin from Pseudomonas aeruginosa and Serratia marcescens. Reduction of endotoxin was assessed in terms of biological activity, expressed in endotoxin units. Endotoxin concentrations were determined using the Limulus amoebocyte lysate kinetic turbidimetric assay. Glass bottles were inoculated with a theoretical 5000 endotoxin units of one of each of the three types of endotoxin and were subjected to dry heat. Positive control results indicated initial endotoxin concentrations. Successful depyrogenation, defined as a three-log reduction in endotoxin, was achieved for all samples subjected to dry heat. No significant difference was detected in the destruction of endotoxin from the three different bacterial species. This indicates that E. coli endotoxin is a suitable standard for the qualification of depyrogenation processes.

Key words: Depyrogenation, endotoxin, dry heat.

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Rouging in stainless steel equipment for hygienic services

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Stainless steels are one of the most versatile and widely used materials for the construction of domestic and industrial hygienic equipment. The biopharmaceutical industry makes extensive use of Type 316L equipment, taking advantage of the alloy's good formability and weldability required in making a wide range of process equipment. Type 316L also has excellent corrosion resistance for environments encountered in biopharmaceutical applications. However, one form of light corrosion of stainless steel, called rouging, is sometimes encountered in high-purity water systems. Rouge is receiving considerable attention from the American Society of Mechanical Engineers (ASME) Bioprocessing Equipment (BPE) Subcommittee on Surface Finishes as well as from other organisations, but industry still does not have all the answers. This article reports on what is known about rouging and corrective measures to minimise it. The advantages of improved, smoother surfaces through electropolishing are also discussed.

Key words: Rouge, stainless steel, iron oxide, electropolishing, high-purity water system.

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Content and Abstracts

Development of the Russian standard for air quality in hospitals

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It is well known that staying in hospital can be potentially dangerous to health. One reason for this is intrahospital infections, including those caused by micro-organisms that have adapted to traditional hygienic measures and have become resistant to antibiotics. It is therefore important to develop state-of-the-art standards for air cleanliness in hospitals that could serve as practical guides for design and testing of different rooms depending on their purpose. Some existing European standards and the new Russian standard on air cleanliness in hospitals, developed by ASENMCO, are discussed here. When developing the Russian standard, we had to address the following key issues: classification of hospital rooms depending on their purpose (the standard sets five groups of rooms); the criterion for assessment of air cleanliness

(particles, micro-organisms or both); cleanroom occupancy state for specifying requirements; particle size; basic requirements for providing air cleanliness (cross-sectional area of unidirectional airflow; velocity of unidirectional airflow; air exchange rate; types of air filters); and test methods.

Key words: Russian standard, air cleanliness, hospital, particle size, micro-organisms, filter

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Cause-effect analysis for the chemical calibration failures of USP-I and USP-II dissolution apparatus

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This work reviews and analyses each of the factors that can affect the USP-I and USP-II dissolution tests and the calibration thereof. The aim is to assist with the understanding and solving of problems that arise in connection with this analytical technique, which is of great importance to manufacturers of solid dosage forms. This article provides a set of recommendations on issues not addressed by the USP. The authors believe these important points, based on their own experience, should be taken into account.

El presente trabajo es una revisión y análisis de cada uno de los factores que pueden influir en el ensayo de disolución USP-I y USP-II, así como de su calibración. Se busca así una mejor comprensión y ayuda a la resolución de problemas relacionados con está técnica analítica, muy importante en los laboratorios farmacéuticos fabricantes de formas farmacéuticas sólidas. Este artículo a diferencia de otros trabajos, informa de una serie de recomendaciones no contempladas por la USP pero que creemos que son importantes a tener en cuenta y que está en basada en la experiencia de los autores.

Key words: Dissolution, calibration, USP-I, USP-II, degassing, paddles, baskets, vessels, temperature, wobble, shaft centring, levelling, vibration.

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Delivering drugs to the colon using Colal®: a modified-release delivery system

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The development of targeted oral drug delivery systems to the colon has been a challenge for many years. To be successful, the delivery system should be designed to prevent drug release within the upper gastrointestinal tract (GIT) and allow drug release in the colon. Various approaches have been employed dependent upon gastrointestinal pH, transit time of the delivery system through the GIT, luminal pressure within the colon and action by colonic bacterial enzymes. Many of these systems have progressed no further than completing feasibility studies. This article presents the key development work and clinical studies for the Colal delivery system, which relies upon the digestion of glassy amylose, within the coating of the delivery system, by colonic bacterial enzymes to release a drug from the internal core into the colon. The corticosteroid, prednisolone sodium metasulfobenzoate, has been incorporated into the Colal delivery system to provide a new oral treatment for ulcerative colitis (Colal-Pred), which is currently in phase III clinical studies.

Key words: Colal delivery system, Colal-Pred, glassy amylose, prednisolone sodium metasulfobenzoate, colonic delivery

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An intranasal thermoreversible mucoadhesive system of atenolol with enhanced permeation

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The aim of this investigation was to prepare an intranasal thermoreversible mucoadhesive system of atenolol having suitable solubility, enhanced permeation and longer nasal retention. The formulations were composed of different concentrations of chitosan hydrochloride and sodium β-glycerophosphate with 5% hydroxypropyl β-cyclodextrin (HPβ-CD). The samples were characterised for viscosity, gelation temperature, mucoadhesive force and duration of mucoadhesion. In vitro release and in vivo permeation were investigated using a two-chamber diffusion cell, while histological study was performed using porcine nasal mucosa. Addition of 5% w/w HPβ-CD resulted in increased solubility of atenolol from 16mg/ml to 60mg/ml. Addition of
β-glycerophosphate to formulations induced temperature-mediated phase transition at 35 ± 1°C. Increase in concentration of chitosan hydrochloride was found to elevate the bioadhesive force of formulations. Nasal permeability of atenolol (3.68 x 10-6cm/s) was greater than intestinal permeation (2.92 x 10-6cm/s), and was further enhanced with the inclusion of chitosan hydrochloride and
HPβ-CD (9.17 x 10-6cm/s). The intranasal thermosensitive system containing chitosan hydrochloride and HPβ-CD provided enhanced permeation through nasal mucosa due to a synergistic effect without any destructive effect.

Key words: Intranasal thermoreversible system, atenolol, chitosan hydrochloride, hydroxypropyl β-cyclodextrin, in vitro permeation.

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A mathematical approach to assessing temperature excursions in temperature-controlled chains

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More and more products are distributed by the temperature-controlled chain. It can happen that products are subjected to temperature excursions. The decision to release them is often based on subjective arguments. This paper presents a mathematical model that could be used to assess the temperature excursion effect on the potency of the product.

Key words: Drug, distribution, temperature excursion, mathematical model, cold chain, temperature-controlled chain.

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GMP and sterile filtration: a review of some practical and regulatory issues

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An increasing number of regulatory references and comments relating to double sterile filtration and redundant sterilising filtration, and generally the need to use two sterilising grade 0.2µm filters in series in aseptic processes, has led to a degree of confusion over what these expressions actually mean in terms of location and practicalities of using these filters.
In an attempt to clarify some of these terms, the Pharmaceutical and Healthcare Sciences Society Working Group on Process Filtration has reviewed and applied the group's interpretation to a number of the terms commonly used by filter manufacturers, filter users and regulatory bodies.
This paper does not discuss issues relating to sterile vent filters, which have been addressed elsewhere.1

Key words: filter, liquid, sterilising, bioburden reduction

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Deviation management in the context of ICH Q9/Q10

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ICH Q9 Quality Risk Management working party of the Quality Assurance Committee of the Catalan Section of the Spanish Association of Industrial Pharmacists (AEFI)

The Spanish Association of Industrial Pharmacists (AEFI) monograph ICH Q9 Quality Risk Management not only describes the general principles of risk management set out in that guideline, but also takes an approach that is highly practical for the pharmaceutical industry. It therefore contains examples of how to use various risk analysis tools, including definitions, usage, objectives, operation, and advantages and disadvantages in each case. This article forms part of one of the examples of the use of failure mode and effects analysis (FMEA) risk analysis tools.

En la monografía de AEFI Gestión de los riesgos de calidad ICH Q9 además de recoger los principios generales de Gestión de Riesgos desarrollados en esta Guideline, se ha realizado una aproximación eminentemente práctica para la industria farmacéutica. Por ello se presentan ejemplos de aplicación de las diferentes herramientas de análisis de riesgos incluyendo su definición, aplicación, objetivos, operativa y ventajas e inconvenientes en cada uso. Este artículo forma parte de uno de los ejemplos de aplicación de las herramientas de análisis de riesgos FMEA (failure mode and effects analysis).

Key words: ICH Q9/Q10, risk management, critical and non-critical deviations, flowchart, failure mode and effects analysis.

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Reprocessing reject batches from a design space perspective

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When a batch is rejected there is a possibility of recovering it in accordance with Good Manufacturing Practice guidelines. Various general procedures are described, for use when

specific types of formulations fail to meet their specifications. The ideas contained in the new International Conference on Harmonisation quality guidelines are worthy of inclusion, as they place reprocessing on a good scientific basis and define a three-level design space that allows analysis of the risks involved.

La aparición de un lote rechazado plantea la posibilidad de su recuperación según las Normas de Correcta Fabricación. Se mencionan diversos procedimientos generales de aplicación al incumplimiento de especificaciones para cada tipo de formulaciones. Resulta interesante incorporar el concepto de las nuevas normativas de calidad de la ICH y así su reprocesado presente una adecuada base científica y defina un espacio de diseño en base a tres niveles que alcance un análisis de los riesgos implicados.

Key words: ICH, manufacture, rejection, reprocessing, out-of-specification

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Headspace analysis: a predictive tool for stopper/vial compatibility

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Component choice for lyophilised products does not appear to include consideration on the preservation of the headspace during the lag time between stopper insertion and application of the overseal. The aim was therefore to find a suitable method that will allow formulators and process scientists to evaluate prospective pack components for compatibility with respect to headspace preservation. Two gas analysis techniques were evaluated: helium leak detection and oxygen analysis using frequency-modulated laser spectroscopy. Three vial conformations of nominal 10ml volume and six rubber stopper formulations with either a helium-rich or 5 x 104 Pa nitrogen headspace were used. Analysis of leak rates and oxygen ingress showed that both systems were very sensitive and ideal for demonstrating which pack components were compatible. Oxygen analysis was preferred due to its simplicity, low cost and the fact that it is directly applicable to conditions seen with typical lyophilised products. A final observation was made on the applicability of the microbial ingress test. Comparison of leak rates and the relative sizes of helium, oxygen and Brevundimonas diminuta showed that demonstration of gaseous integrity would be a good predictor for microbial integrity.

Key words: Container-closure integrity, helium, oxygen, headspace, lyophilised products, component compatibility, pharmaceutical development

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Content and Abstracts

Monitoring efficiency of microbiological impaction air samplers

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In cleanrooms the main source of biocontamination is people. The concentration of airborne biocontamination depends upon the number of people present in the cleanroom, their level of activity and the clothing system used.
In controlled areas the cleanliness of the supply air may be the same as that in the critical areas but processes and people cannot be controlled so rigidly. Microbiological methods used for monitoring air in controlled areas, eg. during operational or dynamic states, should be able to measure both high and low concentrations of airborne micro-organisms.
There are several methods of measuring the airborne contamination and many published reports show that the results – expressed as the number of colony-forming units per cubic meter (CFU/m3) – depend upon the measuring equipment used. The differences in results between microbiological air samplers often depend upon the physical parameters of the samplers. These parameters, together with the d50-value (cut-off size) for impaction air samplers, are discussed. The d50-value is the aerodynamic particle diameter where 50% of the

particles are collected in the sampler and 50% are not collected. In order to predict the collection efficiency of impaction samplers, a simplified mathematical model is presented and examples given. Some design guidelines and a method for evaluation of sampling locations are also presented.

Key words: Impaction sampler, airborne biocontamination, colony-forming units, aerodynamic particle diameter, cleanroom

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Principles and considerations for bubble point and diffusive airflow integrity testing methods for sterilizing-grade filters

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Integrity testing of sterilizing-grade membrane filters is a commonly used and needed non-destructive test to determine whether or not the filter performs as specified or contains a flaw, which would cause microbial penetration. Common integrity tests performed are diffusive flow, bubble point or pressure hold. All these tests have shown reliability and accuracy, therefore any notion of contention of these filter test methodologies would be mistaken. Unfortunately, in some instances, favouritism of a particular integrity test is expressed, which is undesirable and scientifically invalid.

Key words: Integrity test, sterilizing-grade filter, diffusive flow, bubble point, membrane filter.

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Degrees that matter: temperature profiles

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Whatever system is used for the shipment of temperature-sensitive cargo, it will undergo an evaluation and test phase. Its performance is evaluated under test conditions. Temperature profiles, the ambient temperatures during the test, are crucial parameters in these trials.

Key words: AFNOR, cold chain, DIN, insulation containers, ISTA, temperature profiles, test requirements, validation.

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Preparation, characterisation and tableting of solid dispersion of furosemide with crosscarmellose sodium

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This article investigates enhancement of the dissolution profile of furosemide using solid dispersion (SD) with crosscarmellose sodium and a kneading technique. The 1:1 (w/w) and 1:2 (w/w) solid dispersions were prepared by a kneading method using solvent water and ethanol in a 1:1 ratio. Dissolution studies using the USP paddle method were performed for solid dispersions of furosemide at 37 ± 0.5°C and 50rpm in simulated gastric fluid of pH 1.2. Fourier transform infrared spectroscopy, differential scanning calorimetry and X-ray diffraction were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. Tablets were formulated containing SD products and compared with commercial products. Infrared spectroscopy, X-ray diffraction and differential scanning calorimetry showed changes in the crystal structure of furosemide towards an amorphous structure. Dissolution of furosemide improved significantly in SD, the 1:2 SD showed a 5.11-fold increase in dissolution. Tablets containing SD exhibited a better dissolution profile than commercial tablets. Thus, the SD technique can be successfully used for improvement of dissolution of furosemide.

Key words: Solid dispersion, furosemide, crosscarmellose sodium, dissolution enhancement, fast-dissolving tablets.

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