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Content and Abstracts

Calculation of the number of surviving spores on biological indicators which survive half-cycle gaseous sterilization processes

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Biological indicators (BI) to monitor the effectiveness of sterilization are described in the European Pharmacopoeia1 as well as in other reference texts. In the European Pharmacopoeia, sterilization parameters for moist (121°C/15 min) and dry heat sterilisation (160°C/2 hrs), and for sterilization by irradiation (25 kGy) are described. The parameters described ensure the adequate and safe sterilization of the goods to be treated, and take into consideration that a sterility assurance level (SAL) of 10-6 or below must be achieved.

Sterilization using the parameters mentioned above means that routine use of biological indicators to monitor the effectiveness of sterilization is not necessary in these cases.

Therefore, the use of biological indicators is mandatory only in the case of gaseous sterilization, e.g. ethylene oxide, formaldehyde and hydrogen peroxide. The knowledge of the D-value of these biological indicators might be useful for determining the adequate gas exposure time required to kill the spores on the indicator completely, which indicates that the sterilization was effective. However, the certified D-value is only valid under exactly defined sterilization conditions. These conditions under which the D-value was determined are often different from those in routine sterilization. If the conditions are different, the D-value must be re-determined under routine sterilization conditions. The European standard, EN 866, specifies how the D-value(s) is or are to be determined in such cases. These normative requirements are difficult to implement in practice. In such cases, a “combination” of practical considerations and normative requirements should be used to identify solutions in individual cases.

Key words: Biological indicators, most probable number of surviving spores, half-cycle method, Poisson distribution, D-value

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Moist heat resistance evaluation of Clostridium sporogenes and Geobacillus stearothermophilus on various carriers in order to meet the European Pharmacopoeia 5, Section 5.1.2 Biological Indicators of Sterilization

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There is a variety of biological indicator (BI) organisms used for the evaluation of moist heat sterilization processes. These organisms include Clostridium sporogenes, Bacillus atrophaeus, Bacillus coagulans and Geobacillus stearothermophilus. Their resistance to moist heat varies from organism to organism as well as from carrier to carrier. B. atrophaeus is used to detect dry heat conditions in a moist heat sterilization process. Studies were conducted to compare the moist heat resistance of C. sporogenes (Hospira, Inc. manufactured BI) on various carriers. In addition, commercially available G. stearothermophilus on stainless steel was evaluated under various conditions. Moist heat exposures were conducted in an R&D BIER vessel for screening purposes as well as for triplicate validation runs of the BI itself. Such resistance data were used to arrive at a BI that could be used to support porous load (hard goods) autoclave sterilization in a production facility. The European Pharmacopoeia states that the “spores of G. stearothermophilus are recommended” for steam sterilization. It continues to state that “the D-value at 121°C exceeds 1.5 minutes”. Microbiological studies were performed in order to demonstrate that C. sporogenes could meet European Pharmacopoeia D-value requirements as a BI. This necessitated the screening of various C. sporogenes crops to assure that one is starting out with a BI of high moist heat resistance. Data will be presented that evaluates the moist heat resistance of C. sporogenes and G. stearothermophilus on various carriers and various packaging configurations.

Key words: Porous load, carriers, Clostridium sporogenes, Geobacillus stearothermophilus, D-value, moist heat resistance

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Steam sterilization of filtration systems: practical considerations for in-line operation

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Steam sterilization cycles impose significant stresses on disposable filter cartridges when temperatures approach the melting points of materials used in their construction. Procedures for routine use in a production environment must include an operating safety margin.
For in-line steam sterilization the design of the filter system and services influences the suitability of the procedure and the validation effort required.

Uncontrolled sterilizing conditions can occur if the correct operating sequence is not followed, if the system is subject to outside influences or if the filter condition during sterilization is unknown, thus leading to filter damage or process failure.

Operating principles established for a simple filter system are systematically applied in method development for more complex process configurations, such as double filtration systems or simultaneous sterilization of downstream equipment and ancillary service filters.

Operator training is vital to the success of procedures for steam sterilization of processing equipment, in which the sterilizing grade filter is a small but important part. Training should include clear instruction on Standard Operating Procedures and detailed understanding of the underlying principles. This allows operators and software engineers (for system automation) to recognise the factors in their system design that control a safe and successful sterilization regime.

Presented in a workshop during The Parenteral Society Annual Conference at the Renaissance Solihull Hotel, UK, on 9 November 2005

Key words: Steam sterilization, Membrane filter, Double filtration, In-line

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Aspects of the preservative requirements for multiple dose eye care products

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The preservation of multiple dose ophthalmic solutions is one of the more crucial aspects of the formulation development of these products, and in particular the need to meet the antimicrobial efficacy requirements imposed by the pharmacopoeias.

The primary purpose of the inclusion of a preservative system is to prevent patient infection during the use of the product. The secondary purpose is to prevent microbial spoilage of the product once the pack has been opened. The toxic or allergic potential of the available preservatives must be kept in mind. The levels used should therefore be the minimum needed to achieve

adequate protection of the patient and the product without inducing adverse reactions in the user1.

Key words: Ophthalmic solutions, preservative efficacy, adverse effects, ocular infections

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Effect of white pulsed light on Pseudomonas aeruginosa culturability and its endotoxin when present in ampoules for injectables

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In the present study we show that exposure to one flash of white pulsed light of a population of Pseudomonas aeruginosa (106 CFU/ml) contained in a sealed glass ampoule for injectables is sufficient to reduce to zero the culturability of these bacteria. However, the use of fluorescent markers of cell death and the application of a revival technique in the presence of nalidixic acid reveals that after this treatment, viable but non-culturable forms of P. aeruginosa can be present in the sample, although any attempt to recover culturability was unsuccessful, suggesting that these bacteria had entered in an irreversible process of cell death. When lipopolysaccharide from P. aeruginosa was submitted to several flashes of pulsed light, no change in the endotoxic activity of the molecule was noted when a low concentration solution (0.1 ng/ml) was used. In contrast, using a highly concentrated solution (50 ng/ml) we observed an increase of the endotoxic effect of the extract. These results show that white pulsed light can be efficiently employed for sterilization of ampoules for injectables containing low levels of contaminated material but should not be applied in the same conditions to untreated or highly contaminated samples.

Key words: Rapid decontamination techniques, Viable but non-culturable bacteria, Lipopolysaccharide, Pharmaceutical industry, Bacterial stress, Sterilization

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Microbial identification using a sequencing-based system: bacterial and fungal case studies

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The analysis of the 16S and the LSU rRNA gene sequences represents a genotypic alternative for bacterial and fungal identification, respectively. The commercially available sequence-based MicroSeq® systems for microbial identification are presented through their application to bacterial and fungal case studies. Isolates of the bacterial Methylobacterium genus and of the fungal Fusarium genus have been chosen because of their relevance in pharmaceutical environment monitoring. They are known to be extremely hard to identify by conventional phenotypic methods, even at the genus

level. Comparative analysis of the first 500 nucleotides of the 16S rRNA gene of type species of Methylobacterium and type species of 12 closely related genera showed very high intergenus sequence variations (>5%). Moreover, for type strains of 15 validly described species, divergences in the 16S rRNA sequences allowed for their clear distinction. Case studies corroborate that Methylobacterium spp isolates (n>40) can readily and reproducibly be identified down to the species level using sequencing based analysis with this system. Similarly, analysis of the second domain of the LSU rRNA gene of known Fusarium spp and closely related genera showed distinguished intergenus and interspecies sequence differences. Case studies confirmed that Fusarium spp isolates (n>30) can be identified at the genus level, and even down to the species level, using sequencing based analysis.

Key words: Bacterial and fungal identification, Genotypic method, Environmental isolates

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Burkholderia (Pseudomonas) cepacia – A brief profile for the pharmaceutical microbiologist

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There is a substantial amount of evidence, including recent fatalities, to support the view that the pharmaceutical industry should be concerned over the potential contamination of non-sterile dosage forms by Burkholderia cepacia. It is not one of the micro-organisms named in the pharmacopoeias against recommendations to use selective media to confirm absence from non-sterile products, and few, if any, pharmaceutical quality control laboratories ever attempt its selective isolation. It is suggested that because of this the occurrence of Burkholderia cepacia in pharmaceutical products may well be under reported. Nonetheless, selective media have been developed for isolation of Burkholderia cepacia from clinical specimens and it is suggested that there is enough information available from these other media to allow development of suitable selective media for pharmaceutical applications.

Key words: Burkholderia cepacia, Pseudomonas cepacia, Respiratory disease, Selective isolation, Objectionable micro-organisms, Commercially available media

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The clean status of a refined steel surface and related measuring techniques

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The cleanliness/contamination of a refined steel surface raises a whole series of specific questions and recontamination/cleanliness can frequently extend as far as significant surface damage. Surface damage can certainly be prevented by selecting the appropriate chemical and physical cleaning/purification methods and also by paying attention, in each case, to the final refined steel surface structure of the component surface.

Die Reinheit/Kontamination einer Edelstahloberfläche wirft eine ganze Reihe von fachspezifischen Fragen auf, wobei eine Rekontamination/Reinigung in Grenzbereichen häufig in den Bereich der (massiven) Oberflächenbeschädigung hineinreichen kann. Bei der Wahl der chemisch und physikalisch passenden Reinigungsmethode muss zur Vermeidung der Oberfläschenbeschädigung beim Reinigen zudem in jedem Falle auch die endgültige Ausführung der Edelstahloberfläche des jeweiligen Bauteils in Betracht gezogen werden.

Key words: Austenitic alloys, Refined steel, Contamination

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Control of cold chain distribution

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Increasingly new medicinal products are sensitive to temperature and require specialised storage and distribution. The regulatory authorities are becoming concerned about the quality of the distribution chain for these products. In addition to the EU guidelines on Good Distribution Practice of

Medicinal Products for Human Use (94/C 63/03), the MHRA, USP, Health Canada, WHO and the IMB have either issued or have draft guidelines in preparation. There are two ways to maintain a specific temperature during transport. There are “passive” systems which rely on insulation and phase change material e.g. ice and alternatively “active” systems such as refrigerated vehicles and specialised containers designed for air freight. The transport and storage of temperature sensitive medicinal products should be considered to be part of the GMP quality system as far as possible. It should be controlled by standard operating procedures and quality agreements between the manufacturer and all service providers. The aim is to provide the patient with the same quality of product that was released on to the market by the QP at the end of the manufacturing process.

Key words: Good distribution practice, cold chain, temperature sensitive products

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Bacterial diversity of the contaminants of hard gelatin capsules using numerical profiles and conventional methods

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Hard capsules are made of gelatin produced by acid or alkaline hydrolysis of animal collagen. Many types of bacteria are known to survive the various stages of gelatin production process and are usually detected in finished gelatin granules. However, compendial specifications for hard gelatin capsules are not available. The pharmaceutical industry usually have in-house limits and control procedures to check the microbiological quality of these capsules before being used.

In this work, the bacteriological quality of 10 batches of hard gelatin capsules used by a pharmaceutical company in Jordan was investigated. Salmonella species, Escherichia coli and Staphylococcus aureus were not detected, but Pseudomonas aeruginosa was recovered from 1 batch. Two batches were found to be free of bacterial contamination and those which were contaminated, harbored bacteria in counts <103/gram.

To establish the diversity of the bacterial population contaminating the capsules, 80 isolates were purified and their characters determined using 12

conventional tests. A 4-digit numerical profile was generated for each isolate. The most frequently encountered profile was 5733 and this profile was detected in six capsule batches. Dominant bacteria were gram-positive spore-forming rods. It is concluded that the majority of the bacterial contaminants of hard gelatin capsules were probably acquired from the gelatin granules used in their manufacture.

Key words: Hard gelatin capsules, Contaminants, Bacterial diversity, Numerical profiles

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The use of polymeric flooring to reduce contamination in a cleanroom changing area

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This paper describes a study undertaken in a biopharmaceutical manufacturing facility, within the National Blood Service as part of The National Health Service and located in the south-east of England. The study centred on the reduction of microbial contamination from the footwear of staff and trolley wheels where they access a first-step change area. The study demonstrated that microbial counts into the access corridor significantly reduced, by approximately 80%, following the fitting of polymeric flooring. Therefore polymeric flooring can be a useful addition to a contamination control programme.

Key words: Microbial counts; environmental monitoring; surfaces; particulates; polymeric flooring

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Containment system integrity – sterile products

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Sterility is an unnatural condition; for sterile pharmaceutical dosage forms sterility is maintained only by the integrity of their containment systems. Despite regulatory requirements for the microbiological integrity of containment systems to be demonstrated through the shelf-lives of sterile dosage forms, there is no standard test and no standard acceptance criteria. However, liquid immersion microbiological challenge tests have come into general use as the method of choice. This paper discusses the parameters described in various papers for this test. These include the choices of challenge micro-organisms, challenge concentrations, contact times, numbers of challenged containers, challenge conditions, incubation and controls. The difficulties associated with demonstrating the microbiological integrity of containment systems at the end of shelf-life are also discussed.

Key words: Sterile products, containment, micro-biological challenge test, micro-biological integrity, liquid immersion, stability programmes

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Formulation of aqueous norfloxacin solutions for parenteral use

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The purpose of this study was to formulate norfloxacin 8% aqueous stable solutions for parenteral use. Forty formulations were prepared and norfloxacin targeted solubility was achieved by forming organic/inorganic acid or basic salts in situ. Acetate and phosphate buffer (pH 2.45-10.0) were added to some formulations. Glycine and propylene glycol were used in some formulations as auxillary buffer and as cosolvent. The prepared formulations were initially assessed over a six-month period for their precipitation tendency during storage at 25°C. Promising formulations were further subjected to 12 months physical and chemical stability evaluation. Compatibility of freshly prepared formulations with some intravenous fluids was also tested.

36 out of 40 formulations showed signs of turbidity. Incompatibility was detected between norfloxacin cation and phosphate ion. Four formulations, containing acetate buffer (pH 2.57-3.92) remained clear over four years. Formulations stored in colourless glass under indirect sunlight showed evidence of chemical degradation. Heat alone (60°C) did not adversely affect norfloxacin stability in the four promising formulations.
Resistance of stable solutions toward precipitation appears basically due to the existence of norfloxacin as a mixture of two salts, hydrochloride and acetate. The four stable norfloxacin solutions have potential parenteral application in the human/veterinary fields.

Key words: Norfloxacin, injections, salts, solubility, stability

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Mouthwash contaminated with Burkholderia cepacia

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Burkholderia cepacia is a ubiquitous micro-organism with special metabolic properties. It has been described as a pathogen in humans, particularly in cystic fibrosis patients. Its presence has also been reported in human medicines and in personal hygiene products. The present paper describes an investigation carried out on a mouthwash contaminated with B. cepacia which caused an outbreak of respiratory infection in a hospital in the Canary Islands (Spain). Results demonstrate that the outbreak was caused by a mouthwash contaminated with B. cepacia, produced by a manufacturer that did not follow GMPs. Restrictions imposed on the company prohibiting further sales resulted in the manufacturer being forced to implement GMPs and to perform the corresponding official controls.

Burkholderia cepacia es un microorganismo ubicuo que tiene unas propiedades metabólicas específicas. Ha sido descrito como un patógeno en humanos en grupos especiales de pacientes como los enfermos de fibrosis quistica. También se ha descrito su presencia en diferentes medicamentos de uso humano y en productos de higiene personal. En esta comunicación se describe la investigación realizada en un colutorio contaminado por B. cepacia que provocó un brote de infección respiratoria en un hospital de las Islas Canarias (España). Los resultados demuestran que el brote fue producido por una cepa de B. cepacia presente en un colutorio fabricado en una empresa que no cumplía con las buenas prácticas de fabricación (GMP). La medida tomada de prohibir la comercialización del producto, condujo a que la empresa implicada aplicara las normas de buenas prácticas de fabricación y realizara los correspondientes controles oficiales.

Key words: Burkholderia cepacia, contaminated mouthwash, respiratory infection

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Keratin proteins as an indicator to monitor human particle contamination in cleanrooms

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In this report, we describe fast, convenient, and sensitive methods for monitoring human contamination on surfaces and aerosol sedimentation

samples in cleanroom environments. Different protein chemistry approaches were evaluated and optimised for the measurements of keratinous material. Fluorescence-based assays were chosen for their sensitivity and rapid applications. Gel electrophoresis (SDS-PAGE) was used for protein characterisations. Six different gel visualisation techniques were tested. Keratin polypeptide segments were terminated with immunoblotting. Human particle loads in sedimentation samples were determined as direct microscopy counts of FITC-labelled skin cells. The samples were collected from both cleanrooms and ordinary rooms for comparison purposes. The total background particle distribution was measured according to ISO-14644:1999 standard with an optical particle counter. The data obtained shows that keratin is a sensitive indicator of human activity in cleanroom facilities. The described methods can be used to monitor human particle distributions and critical contamination areas in the cleanroom environment. The observed data can be utilised in development and as a troubleshooting tool to ensure optimal cleanroom operations.

Key words: Cleanroom, SDS-PAGE, immunometry, fluorescent microscopy, FITC-label, monoclonal antibody

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Regulating the use of disinfectants and human hygiene products in Europe: The Biocidal Products Directive 98/8/EC

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This paper describes how the Biocidal Products Directive 98/8/EC controls the supply and use of human hygiene biocidal products, such as hand sanitisers, private area and public health area disinfectants and other biocidal products. These are products used for the disinfection of air, surfaces, materials, equipment and furniture (which are not used for direct food or feed contact) in private, public and industrial areas, including hospitals, as well as products used as algaecides. The Directive describes procedures to establish a positive list of active substances which may be used in biocidal products. There is a review program to decide which active substances can be placed on the list for each product type. When a decision is made not to include a substance in Annex I, products containing it can no longer be supplied or used.

For human hygiene biocides, such as hand sanitisers and general industrial disinfectants, the first cut-off date is

1st September 2006. Products that contain “identified” active substances that were not “notified” cannot be supplied or used after that date. The likely cut-off date for these types of products that contain “notified” active substances but for which no technical dossier was submitted to support Annex I listing of the substance is March 2008.

Users of human hygiene products and general disinfectants concerned about the compliance status of the products should check with suppliers before either of these dates to confirm that the products they use will meet the requirements of the regulations.

Key words: Disinfectants, Hand Sanitisers, Biocides, Regulation, Biocidal Products Directive

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Aseptic, pyrogen-free spray drying for injectable, stable liquid drugs and vaccines

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Drugs and vaccines stabilised in dry sugar glasses lose no potency over years at high ambient temperatures. These glasses require reconstitution with water before injection. By producing the stabilised vaccines in water-soluble glass microspheres, they can be suspended in equally stable and inert anhydrous injectable liquids in which they do not dissolve. These are instantly injectable shelf-stable liquid suspensions. By blending selected glass-forming ingredients together, the density of the microspheres produced in a conventional spray dryer can be closely matched to that of the suspending liquid to yield suspensions with neutral buoyancy that neither sediment nor float on storage. This technology has been proven to yield highly immunogenic vaccines which are stable at 37°C for at least three years and also resistant to freezing and high temperatures up to 70°C. A full cGMP plant incorporating a new design of spray dryer which is self sterilising and self de-pyrogenating has been built and clinical trials with pharmaceutical grade stable liquid vaccines begin in 2007.

Key words: Stable liquid vaccines, cGMP spray dryer, density matched suspensions, glass stabilisation, injectable oils, fluorocarbon liquids.

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Using Braille on pharmaceutical packaging

Martin Wesch

Wesch & Buchenroth, Stuttgart, the Quality Association for Pharmaceutical Packaging – QAPP - (Gütegemeinschaft Pharma-Verpackung e.V.) Stuttgart and the team of packaging experts from the International Association for Pharmaceutical Technology in Mainz (Arbeits-gemeinschaft für Pharmazeutische Verfahrenstechnik e.V (APV))

Recently implemented European guidelines require that pharmaceutical packaging must now include a description of the product to be printed in Braille. In addition, package inserts suitable for blind or visually-impaired persons may also be required. However, there are a number of exemptions to this provision that are discussed in this article.

Key words: Pharmaceutical packaging, Braille, EU guidelines, exemption provisions

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