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Contents and Abstract

Blocking of the polyphosphoinositide transmembrane signalling system is a novel and promising approach for AIDS therapy

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It is now evident that even prolonged and aggressive treatment with combinations of antiretrovirals alone will not lead to HIV eradication and a complete cure. Recent studies indicate that the infection will persist for life, even in patients on effective anti-retroviral therapy. Some of the major reasons for that include the inability of the drugs to stop virus replication completely, their high toxicity and the creation of drug resistance leading to fast viral rebound and transient therapeutic effect. Here we show that blocking of the polyphosphoinositide transmembrane signalling system of HIV target cells by lithium in combination with antiretroviral(s), both requiring obligatory encapsulation in liposomes, overcomes most of the routinely used therapy drawbacks. The extended preclinical and pilot clinical trials evaluating our preparation FTL/AZT/PEBA, based on the above approach, reveal that it is not toxic and may contribute considerably to successful AIDS therapy and the prevention of HIV-promoted malignant transformation.

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An evaluation of the effectiveness of polymeric flooring compared with “peel-off” mats to reduce wheel- and foot-borne contamination within cleanroom areas

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It has been established that, in order to maintain the highest levels of cleanliness within a cleanroom environment, it is essential to prevent the ingress of particles and micro-organisms into the critical area from the surrounding environment. Principles of good manufacturing practice (GMP) and quality assurance demand that particle and microbiological contamination levels within any critical area should be minimised to prevent

contamination entering the product. Two major sources of viable and non-viable particle contamination entering critical environments are from operators' feet and trolley wheels. This paper compares two different types of floor covering used to reduce foot- and wheel-borne contamination, namely the "peel-off" acrylic mat and "polymeric" floor covering. The results of this comparison demonstrate that "polymeric" flooring is a more effective means of controlling foot- and wheel-borne contamination, thereby effectively reducing the number of micro-organisms entering the critical environment.

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Young scientist award 2001

The design and development of a pharmaceutical isolator

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Isolators for use within the pharmaceutical industry must protect both the product and the users from contamination. A flexible film envelope with a negative pressure environment creates a suitable barrier method.

This paper examines the design and development process of a pharmaceutical flexible film isolator. A major consideration at the design stage is the ease of use of the final product in its application, where ergonomic factors are included in the design specification. Coupled with this, the manufacturing process must also be optimised. Following design and development, the isolator is manufactured, utilising Computer Aided Design / Computer Aided Manufacture (CAD/CAM) technology.

In this study, the product design and development stages are discussed, in terms of customer and user requirements, and also from the viewpoint of aiding the manufacturing stage. An important part of this process is obtaining customer feedback, in order to determine any design changes necessary for future isolator manufacture.

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Young scientist award 2001

Pharmaceutical water storage and distribution design

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This paper presents and discusses the key characteristics of validated water storage and distribution systems to attain compliance with water quality, whilst retaining optimum system performance. Pharmaceutical water system design has been developed, drawing on influences from regulatory bodies and current process design issues. The following discussions evaluate storage and distribution systems, covering common system configurations, from the storage tank through to the user point. Particular focus is placed on fundamental design criteria required to meet and maintain pharmaceutical standards.

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Contents and Abstract

Pharmaceutical technology study on binary mixtures (injectable lipid emulsion – glucose) for potential use in total parenteral nutrition

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A study was carried out on the physical stability of binary injectable lipid emulsion (ILE)-glucose mixtures obtained by the inclusion of glucose in the aqueous phase of the system during the emulsion process. These results were compared with results obtained using mixtures of similar composition

obtained by the extemporaneous admixture of glucose solution to a previously prepared ILE solution, which is the method normally used by hospital pharmacy services when preparing complex mixtures for parenteral nutrition. The results demonstrate conclusively that incorporation of glucose in the system at the preparation stage increases emulsion stability even following system sterilisation.

Se estudia la estabilidad física de mezclas binarias emulsión lipídica inyectable (ELI)-glucosa obtenidas por inclusión de ésta última durante el proceso de formación de la emulsión, a la fase acuosa del sistema. Los resultados se comparan con los de mezclas de análoga composición obtenidas por adición extemporánea de soluciones de glucosa a la ELI previamente preparada, técnica seguida habitualmente en los servicios de farmacia de los hospitales para la preparación de mezclas complejas para nutrición parenteral. Los resultados obtenidos permiten concluir que la incorporación de la glucosa al sistema en formación incrementa su «efecto protector» incluso tras el proceso de esterilización del sistema.

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Needlestick injuries and infections: an overview

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Healthcare workers who use hypodermic needles are at risk of accidentally pricking or stabbing their fingers or hands. The injury may be slight, but if the needle is infected with one of the blood-borne diseases, there is the possibility of transferring the agent of that disease to the worker. This brief review examines the mechanisms and risks associated with such 'needlestick' injuries and infection and the precautions that may be taken to minimise them. References are given to more detailed works on the subject.

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Contamination control clothing – selecting a system to meet your requirements

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Cleanroom clothing forms a critical part of the contamination control strategy required in cleanroom production areas. This review article outlines the main areas for consideration when selecting an appropriate garment regime.

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A cleanroom contamination control system

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Analytical methods for hazard and risk analysis are being considered for controlling contamination in pharmaceutical cleanrooms. The most suitable method appears to be the HACCP system that has been developed for the food industry, but this requires some reinterpretation for use in pharmaceutical manufacturing. This paper suggests a possible system. To control contamination effectively, it is necessary to have a good appreciation of the routes and sources of contamination, and the means of controlling them. An overview of these is given.

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Filter pore size versus process validation – a necessary debate?

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Sterilising grade membrane filters, commonly rated as 0.2- μ m and withstanding the ASTM F 838-83 challenge standard, are widely used in biopharmaceutical industry aseptic processes. These filter types have been shown to reliably produce a sterile filtrate in a wide variety of filtration

applications. Instances of microbial penetration through 0.2- μm rated filters, rare as these are, prompted discussion about the universal use of 0.1- μm rated membrane filters to enhance the sterility of the filtered fluid, without first evaluating factors like flow rate, total throughput, non-specific adsorption, extractable components and the real need for tighter filtration.

0.2- μm Sterilfilter die den ASTM F 838-83 Bakterien-beaufschlagungstest bestehen, werden seit Jahren mit Erfolg in den aseptischen Prozessen der biopharmazeutischen Industrie eingesetzt. Diese Membranfilterarten haben vertrauensvoll bewiesen, dass diese in unterschiedlichsten Applikationen ein steriles Filtrat produzierten. Einzelfälle in denen Mikroorganismen den 0.2 μm penetrierten, führten zur Diskussion generell 0.1 μm bezeichnete Filter, unter dem Augenschein einer höheren Sterilitätssicherheit, einzusetzen, obwohl Einflüsse auf die Flussrate, Standzeit, unspezifische Adsorption, extrahierbare Bestandteile und vor allen der wirkliche Nutzen nicht berücksichtigt wurde.

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An overview of viral filtration in biopharmaceutical manufacturing

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Virological safety of biotechnologically-derived and plasma-derived therapeutics is ensured through complementary manufacturing and quality control measures that include control and monitoring of raw materials, validation and implementation of effective virus clearance technology, and monitoring of final-filled product for the presence of virus. Virus filtration, a robust and effective virus clearance technology, is a common unit operation in the manufacture of biologicals. This paper, intended as a basic guide to understanding and implementing virus filtration, discusses the following key topics: modes of filtration, filter ratings and nomenclature systems, virus retention, protein yield, filter sizing and typical filter applications.

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An evaluation of polymeric flooring and its effectiveness in controlling airborne particles and microbes

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A study was carried out to examine the ability of Dycem polymeric flooring to remove particles and microbes from the air in controlled and uncontrolled environments. Test results indicated that the polymeric flooring investigated is most effective in environments containing high numbers of airborne particles and microbes, reducing these potential contaminants by as much as 60%.

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Development of a new multiple-zone prefiltration membrane technology

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This paper describes development of a new microporous membrane structure optimised to extend the service life of sterilising-grade final membrane filters. A unique membrane casting technique has been developed, resulting in a membrane structure with multiple, contiguous zones of varying pore size. The porosity of each zone can be independently controlled to produce a membrane structure optimised for a given feed contaminant profile. The unique membrane structure results in a filter which provides high flow rates together with high bioburden retention and contaminant capacity. The multi-zone membrane can be pleated into a very high area to volume configuration, while maintaining ability to be integrity-tested by users. The performance of this new membrane is compared to existing conventional isotropic and asymmetric membranes with respect to water flow rate, contaminant capacity and bioburden reduction capability with *Brevundimonas diminuta*.

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A critical look at sterility assurance

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This paper reviews a number of closely related aspects of sterility assurance. The poorly understood, but clear difference between "sterile" and "aseptic" are explored. The distinction between them is then reviewed against the practices of aseptic processing, sterilisation, environmental monitoring, parametric release, bioburden testing and sanitisation practice in the industry. It also introduces the subject of "risk" in the context of sterile product manufacture

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Risk assessment with the LR-Method

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It is possible to identify and evaluate potential risks in the form of airborne contamination using the Method for Limitation of Risks (LR Method). This method presents a fast and reliable way of evaluating microbial safety and is a useful tool in risk assessment, e.g. HACCP. The concepts of a) Visualisation of Air Movements, b) the Particle Challenge Test and c) Calculation of Risk Factor, add up to an effective way of identifying potential hazards. It can be used for tracing dispersion routes of airborne contamination, and for the evaluation of single steps of the process.

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Selecting 0.1 or 0.2/0.22-rated filters: Consideration of rates of flow

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Membrane filters of specific pore size are widely used in aseptic processes in the biopharmaceutical industry for the sterilisation of liquid drug products. These filter systems are commonly sized according to their flow rates and total throughput capabilities. Smaller pore size ratings, for example 0.1µm, reduce flow rate due to the finer pore structure, and the required throughput may only be achieved by the use of additional filter elements. This fact has been contradicted by a claim that a particular 0.1µm rated filter has a flow rate as high as a 0.2µm rated filter. This paper explores the physics behind this claim.

In aseptischen Prozessen in der biopharmazeutischen Industrie werden hauptsächlich Membranfilter mit spezifischen Porengrößen zur Sterilisierung flüssiger Produkte eingesetzt. Die Größe eines Filtersystems wird durch die Flussrate und die Standzeit der eingesetzten Filter bestimmt. Kleinere Porengrößen, wie zum Beispiel 0.1 µm, haben geringere Durchflussraten durch die feinere Porerstruktur und daher müssen zusätzliche Filterelemente verwendet werden um höhere Flussraten zu erreichen. Diese Tatsache wurde nun widersprochen durch die Behauptung, dass ein bestimmter 0.1 µm Membranfilter die gleiche, wenn nicht höhere Flussrate hat eines 0.2 µm Filters. Dieser Artikel untersucht die Physik dieser Aussage.

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Validation of a laser scanning cytometer for the microbiology QC release of an antiseptic solution

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A laser scanning cytometer (LSC) was validated for product release of a filterable antiseptic solution. The validation of the LSC was performed over a two-month period using the Total Viable Count and Fungi applications. The first part of the qualification was performed on pure culture in order to validate the analytical performance in terms of linearity, accuracy and precision of the LSC count, as well as the assay detection limit and range of detection. The second part of the qualification involved validation of the product neutralisation and the equivalence study with the reference method. The work demonstrated that the LSC under investigation is at least as sensitive as the reference method and allows the release of the antiseptic solution in four hours instead of five days.

Un cytomètre à balayage laser (CBL) a été validé pour la libération d'un produit antiseptique filtrable. La validation du CBL a duré deux mois et a été réalisée avec les applications pour la détection de la Flore Totale et des Levures-Moisissures. La première partie de la qualification a été effectuée sur des cultures pures afin de valider les performances analytiques du CBL. Ainsi, linéarité, exactitude et précision du dénombrement ont été validés de même que la comparaison avec la méthode de référence. La deuxième partie de la qualification a porté sur la validation de la neutralisation du

produit et l'étude de l'équivalence avec la méthode traditionnelle. Cette étude a montré que le CBL est au moins aussi sensible que la méthode de référence et permet de libérer la solution antiseptique en quatre heures au lieu de cinq jours.

Un citómetro de barrido por láser (CBL) fue validado para el control liberatorio de producto final de una solución antiséptica filtrable. La validación del CBL se realizó durante un período de aprox. dos meses utilizando las aplicaciones Total Viable Count y Fungi. La primera parte de la cualificación se realizó con cultivos puros a fin de validar el funcionamiento analítico en términos de linealidad, exactitud y precisión del recuento con el CBL, así como el límite de detección y rango de detección del ensayo. La segunda parte de la cualificación consistió en la validación de la neutralización del producto y el estudio de equivalencia con el método de referencia. El trabajo demostró que el CBL es por lo menos tan sensible como el método de referencia y permite la liberación de la solución antiséptica al cabo de cuatro horas en lugar de cinco días.

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The unique challenges of manufacturing parenteral nutrition products

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The specificity of the products dedicated to total parenteral nutrition is due to the multiplicity of the components and the large format of the containers. The sensitivity of the ingredients to oxygen, associated with the recommended removal of anti-oxidants, requires an efficient protection from air during the entire manufacturing process. In addition, the incompatibility of certain components with each other can only be solved by using specially designed containers with very specific mechanical properties and whose sterilisation constitutes one of the many manufacturing challenges.

La spécificité des produits de nutrition parentérale totale tient à la multiplicité des ingrédients et au grand format des contenants. La sensibilité des principes actifs à l'oxygène, renforcée avec la recommandation de retrait des anti-oxydants, exige une protection efficace contre l'air pendant tout le processus de fabrication. En outre, l'incompatibilité entre certains

constituants ne peut être résolue qu'avec l'utilisation de contenants spécialement conçus, aux propriétés mécaniques très spécifiques et pour lesquels la stérilisation constitue un des nombreux défis lors de la fabrication.

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