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Contents and Abstract

Application of virus filters to biological products: practical and regulatory considerations*

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The transmission of viruses is a risk associated with the use of plasma- or cell-culture derived therapeutic products. Recently filters have been developed with a pore-size small enough to remove viruses. The application of such filters for increasing virus safety is considered from both a practical and a regulatory perspective.

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* This article is based on a presentation originally given at the Parenteral Society 1st European Conference, The Belfry, Warwickshire, UK.

Optical inspection and integrity testing of ampoules and vials

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A practical, reliable and economical method of validating sophisticated optical control equipment is described. The method relies on hand-made challenge kits, prepared using appropriate methods of current AQL (acceptable quality level) lists such as Military Standard 105E or DIN ISO 2859.

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Effects of temperature stress on the glass quality of ampoules for parenteral drug production

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Type I glass ampoules intended for the filling of Water for Injection USP were exposed to a combination of extended dry heat sterilisation/depyrogenation processes with or without steam autoclave cycles and the effects of the various treatments on pH and conductivity of Water for Injection investigated. Tests on product quality revealed that pH and conductivity increase depending on the time and temperature of pre- and post-processing of the empty ampoule and the finished product, respectively. The final pH and conductivity of Water for Injection is the result of an interaction between glass ampoules and the product solution.
The present study shows that the exposure time of empty ampoules to the heating zone of a depyrogenation and sterilising tunnel and the temperature in the heating zone can vary within wide limits without affecting the quality of Water for Injection in the filled ampoules.

Compared to the average exposure time of 10–14 minutes in the validated standard run, which ensures at least a three log reduction in endotoxins, the time in the heating zone could be increased threefold and the heating temperature varied by more than 30°C above or below the validated standard run, without affecting conductivity or pH of the product solution. However, repetition of standard autoclaving cycles (121°C for 15 minutes), with a prolonged exposure to high temperature during product sterilisation had considerable effects on the investigated parameters of the product solution, expressed as an increase in conductivity and pH.

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Contents and Abstract

Documentation for technical premises in pharmaceutical production

Experiences of the use of photogrammetry and computer-aided design

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The first step in creating up-to-date documentation in pharmaceutical production is to capture "as-built" status; photogrammetrical mapping is a particularly effective method. Using a CAD-system (CAD = Computer Aided Design), recorded data are transformed into a three-dimensional model of all the supply systems. This model provides an up-to-date basis for

reconstruction plans at all times, and also facilitates efficient documentation management. The value of the documentation system has already been confirmed in inspections by the German authorities and the FDA (Food and Drug Administration). It was successfully used to demonstrate that technical premises meet GMP/cGMP standards.

Die Grundlage für eine aktuelle Dokumentation wird durch die Erfassung des Ist-Zustandes erarbeitet, wobei der Einsatz der Fotogrammetrie besonders hilfreich ist. Mit Hilfe eines CAD-Systems (CAD = Computer Aided Design) werden die ermittelten Daten in ein dreidimensionales Modell aller Versorgungssysteme transformiert. Dieses Modell bildet eine ständig aktuelle Planungsgrundlage für Umbauten und ermöglicht gleichzeitig die effiziente Verwaltung der Dokumente. Das Dokumentationssystem bewährte sich bereits bei Inspektionen durch deutsche Behörden und die FDA. Es wurde erfolgreich angewendet, um die Einhaltung von GMP/cGMP-Forderungen für die technischen Gebäudeausrüstungen zu demonstrieren.

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Comparative testing for pyrogens in parenteral drugs using the human whole blood pyrogen test, the rabbit in vivo pyrogen test and the LAL test

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In the present study, the human whole blood test PyroCheck® has been compared with the LAL test and the in vivo rabbit method for pyrogen testing of parenteral pharmaceuticals. The basic methods and strategies for ensuring the quality of the testing procedure are described.

The human whole blood test provides several advantages compared to the established methods according to pharmacopoeial requirements. The test detects not only fever-inducing endotoxins of gram-negative bacterial origin, but also those of gram-positive origin, as well as other components potentially inducing fever in the human body.

Comparison with the rabbit in vivo pyrogen test and the LAL test showed that the commercially available PyroCheck® assay is of practical use to the

pharmaceutical industry, providing usable results and enabling pyrogen testing of drugs that cannot be tested using the standard methods.
Die vorliegende Arbeit beschreibt den vergleichenden Einsatz verschiedener Methoden zur Überprüfung parenteraler Arzneimittel auf fieberinduzierende Verunreinigungen. Die Anwendbarkeit der Methoden und Vergleichbarkeit der Resultate der LAL- Gelbildungsmethode, des in vivo Pyrogentests am Kaninchen sowie eines auf dem Nachweis von Interleukin-1ß beruhenden ELISA unter Verwendung von humanem Blut wird dargestellt.

Die Methode zur Prüfung von parenteralen Arzneimitteln auf fiebererregende Verunreinigungen im humanen Vollblutmodell bietet mehrere Vorteile gegenüber den derzeit etablierten Methoden. So werden nicht nur fiebererregende Substanzen bakteriellen Ursprungs gram-negativer Spezies detektiert sondern auch jene gram-positiver Spezies sowie weitere Komponenten, die im menschlichen Organismus eine Immunartwort auslösen würden.

Im Vergleich zu den etablierten Prüfmethoden des LAL- Tests und des in vivo Pyrogentests werden mit dem kommerziell erhältlichen humanen Vollbluttest PyroCheck® einerseits gleichwertige Resultate erzielt, wobei Arzneimittel, die in den etablierten Tests nicht prüfbar sind, nunmehr auf Pyrogene überprüft werden können.

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Review Article

A modular approach to clean environment design

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The pharmaceutical industry worldwide has changed considerably over the past five to ten years. Mergers, consolidation and legislative pressure have combined to create an environment within which expenditure is more closely scrutinised than ever. Recent mergers have also given rise to an intense period of operational review with each and every facility within the new business structures being thoroughly analysed and assessed. On top of this, the time period within which companies can maximise the return on research investment has shrunk, putting them under increased pressure to get new products to market quickly. This tough environment has a significant impact on new projects.

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Contents and Abstract

Evaluation of cleanroom garments in a dispersal chamber – some observations*

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A newly designed dispersal chamber has been installed at KTH, division of Building Services Engineering. Preliminary tests and comparative studies have been performed in the dispersal chamber on selected clothing systems. The results show the relevance of dispersal chamber testing in the evaluation of cleanroom garments.

*This paper has been presented in part at the 15th ICCCS International Symposium in Copenhagen, May 2000.

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Automated integrity testing of hydrophobic filters based on water intrusion measurements: comparative analysis of a refilling continuous-flow and a pressure-decay batch device

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The water intrusion test (WIT) has become a routine procedure in the pharmaceutical industry as a tool for the in situ integrity testing of hydrophobic filters. During the test, the filter housing is submerged with water and automated devices provide an estimate of the evaporated water flow rate across the filter, i.e., water intrusion rate (WIR). WIR is generally correlated to the filter's bacterial retention rate. Commercially available WIT devices differ with regard to the technique used to measure WIR.
In this paper, we investigated the capacity of a pressure-decay batch device and a refilling continuous-flow device to provide reliable measurements of WIR at various WIRs and initial gas volumes above the filter. Experiments were performed with a model filter system simulating typical conditions of WITs and with a full-scale commercial filter. The pressure-decay batch device consistently underestimated the actual WIR. The error increased with decreasing initial gas volumes above the filter and with increasing actual WIRs. Measured WIR values were as much as 25% and 31% lower than the actual WIR for the model filter system and the full-scale filter, respectively. The refilling continuous-flow device yielded WIR measures in excellent agreement with the actual WIRs with both the model filter system and the full-scale filter, independently of the WIR value and the initial gas volume above the filter.

Der Wasser-Intrusions-Test (WIT) hat sich in der pharmazeutischen Industrie als Routinetest zur in-situ Integritätsprüfung hydrophober Filter etabliert. Während des Testes wird das Filtergehäuse mit Wasser gefüllt und

automatisierte Geräte liefern eine Bestimmung des Wasserdampfflusses über den Filter, die Wasser-Intrusions-Rate (WIR). Die WIR wird im allgemeinen mit der Bakterien-Rückhalterate des Filters korreliert . Kommerziell erhältliche Geräte zur Durchführung des WIT unterscheiden sich in der Technik, um die WIR zu messen.

In der vorliegenden Veröffentlichung wurde die Leistungsfähigkeit eines Druckabfall-Batch-Systems und eines kontinuierlichen Nachfüll-Systems zur zuverlässigen Messung der WIR bei verschiedenen WIRs und Anfangsgasvolumen über dem Filter untersucht. Es wurden Experimente mit einem Modell-Filter-System, mit dem die typischen Bedingungen des WIT simuliert werden konnten, und mit einem kommerziellen Filter durchgeführt. Das Druckabfall-Batch-Gerät unterschätzte konsequent den tatsächlichen WIR. Der Fehler stieg mit geringer werdenden Anfangsgasvolumen über dem Filter und mit steigenden tatsächlichen WIRs an. WIR Messungen waren mehr als 25% bzw. 31% niedriger als der tatsächliche WIR für das Modell-Filter-System und für den kommerziellen Filter. WIR Messungen mit dem kontinuierlichen Nachfüll-System lieferten sowohl für das Modell-Filter-System als auch für den kommerziellen Filter Ergebnisse, die in exzellenter Übereinstimmung mit den tatsächlichen WIRs waren, unabhängig vom WIR Wert und dem Anfangsgasvolumen über dem Filter.

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Cytotoxic pharmaceutical isolators – air flow smoke visualisation testing of a negative pressure isolator

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Air flowing into the working zone of a negative pressure isolator may be unidirectional, turbulent, or a combination of both. Which air flow technique to use has long been an issue of the pharmaceutical industry and isolator manufacturers. Increased concern is due mainly to the rising demand for drug preparation in a more controlled environment such as an isolator. Since unidirectional flow (UDF) systems have proved successful in the cleanroom industry, a system is being developed to model the UDF patterns that occur using different extract systems. Three experimental extract models were used to identify effective ways of keeping UDF without compromising the air

change rate. The results will be used for the further development of the design of negative pressure isolators.

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Opinion Paper

Microbiological leak test of supply pipes for pharmaceutical process water

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In order to ensure that the pharmaceutically relevant properties for high-purity process water are maintained, supply pipes for purified water (Aqua purificata) and water for injection (WFI) must be proof against the entry of contaminants of both chemical (e.g. those due to air contamination) and microbiological origin. A microbiological experiment was performed to examine the integrity of a stainless steel one-way/dead-leg supply pipe with junctions and terminal outlet. The distribution system was filled with nutrient medium, and at least three outlets of the pipe were sampled per day throughout the seven-day experiment. None of the outlet valves showed any contamination. Thus, the pipe remained sterile after being filled with culture medium which is easily accessible to a broad range of microorganisms. The sampling outlet valves facilitate aseptic withdrawal of contents from the pipe, so that neither pipe nor outlets showed any leakages or biofilms.

Um die pharmazeutisch relevanten Parameter für hochreines Prozesswasser kontinuierlich einhalten zu können, müssen die Verteilungssysteme für Reinstwasser (Aqua purificata) und Wasser für Injektionszwecke (WFI) widerstandsfähig gegen chemische oder mikrobielle Kontaminationen sein. Es wird ein mikrobiologische Experiment beschrieben, mit dessen Hilfe die Dichtigkeit eines Stichleitungssystemes zur Verteilung von WFI und der installierten Entnahmeventile demonstriert wird.
Über einen Zeitraum von 7 Tagen wurden täglich dreimal aseptische Manipulationen, d.h. Entnahmen aus dem Verteilunsgsystem, an einem mit sterilem Nährmedium gefüllten Stichleitungsstrang vorgenommen. Das Nährmedium verblieb über den gesamten Zeitraum steril, was als Indiz dafür

zu werten ist, dass die Entnahmeventile mikrobiologisch dicht schließen und der Verteilungsstrang keinerlei mikrobiologische Ablagerungen aufwies.

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VALIDATION SPECIAL ISSUE
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Contents and Abstract

Validation – An historical perspective

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We hold these truths to be self-evident, that all men are created equal, that they are endowed by their Creator with certain unalienable rights, that among these are life, liberty and the pursuit of happiness. (Thomas Jefferson, 1743-1826, slave owner)

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Process validation: regulatory compliance or effective production management?

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Process Validation is a regulatory requirement. As part of Good Manufacturing Practice (cGMP), it supports the intention of ensuring that an Active Pharmaceutical Ingredient (of either chemical synthesis or cell culture / fermentation origin), or formulated Drug Product, meets the requirements for quality and purity which it purports or is represented to possess. From a regulatory perspective, process validation is described as being “the documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics”1. Therefore, provided the pharmaceutical industry establishes a process validation programme which adequately considers all the elements described in the comprehensive regulatory guides, the pharmaceutical industry will have adequately achieved its goal of regulatory compliance and conformance…

Several years ago, this philosophy of equating quality with “conformance to specifications” survived. In today’s market, pharmaceutical companies must embrace a new quality culture aligned to business goals. This culture adopts a philosophy of strategic quality management and performance improvement and, if designed appropriately, process validation in its broadest context is part of this new philosophy. Through Process Control, industry benefits from a reduction in product failure and rejection (Cost of Non-Conformance) and an improvement in product yield and process cycle-time. If considered appropriately, industry also benefits from a reduction in in-process and / or finished product testing (Cost of Conformance) by ensuring a “level of control” appropriate for intended purpose.

Process validation therefore offers the pharmaceutical industry an opportunity to strive towards its goal of profitability and marketability. To ensure success, however, the path to process validation requires a full understanding of the ultimate objective and must start during the stages of

Product Development when a product moves out of the “Proof of Principle” phase and into the “Full Product Development” phase, i.e. at a time in the development programme when phase IIa clinical studies are completing and phase IIb/III clinical studies are being planned.

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Analytical method validation

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Analytical Method Validation is a requirement of the ICH Quality Guidelines (Q2A and Q2B). Guideline Q2A discusses the characteristics that should be considered when validating an analytical method. Guideline Q2B provides guidance and recommendations on the methodology of validation of analytical procedures. The objective of validation of an analytical method is to demonstrate that it is suitable for its intended purpose (e.g. identification, assay, dissolution, degradate/impurity determination).

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Review of validation of cleaning and disinfection

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Cleaning validation is the demonstration of the reproducibility of a cleaning procedure to meet pre-determined scientifically valid limits. The purpose of cleaning is to eliminate, as far as is practically possible, any potential risk to the patient arising from cross-contamination or microbiological contamination of the product. The regulatory view is that the manufacturing company is responsible for using its knowledge of the safety of its products and processes and of the potential risk to the patient in order to set appropriate limits.

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Software contamination control – A challenge for the 21st century

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Contaminated software is software that could contain inaccurate data, errors or bugs, or that has been infected with a virus. The use of contaminated software could result in the adulteration of the final product or possibly cause death, injury, or the loss of property.

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Validation project management

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Good effective project management is crucial to executing a project and bringing it to successful completion within the scheduled timeframe and within budget. There are several factors that can influence the project to either progress and succeed, or decline and fail. A methodical and logical approach is required to address these factors. A well-executed project is one where the approach has a sound and firm infrastructure in place, which provides the basis for successful execution of the project. This infrastructure is discussed in this article.

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The application of steam quality test limits

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Steam quality testing, once the sole preserve of the British National Health Service, is being adopted within the pharmaceutical industry on an increasing scale. The perceived need for such tests varies from company to company and country to country. The purpose of this paper is to relate the impact of poor quality steam to the pharmaceutical sterilisation processes and consider the validity of the test frequencies and limits generally applied.

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