VOLUME 1 NUMBER 1 1996

Contents

Technical and Cost Optimisation of Industrial Scale Aseptic Processing Isolators

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Isolators using various elements of barrier technology are not a new concept, but many potential new applications arise almost daily which

demand careful review and analysis, since they test the limits of the current state of the art and traditionally accepted practice. This is particularly so in the case of aseptic processing in the pharmaceutical industry.

Some Observations on Environmental Monitoring of Cleanrooms

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Common methods for microbiological monitoring in cleanrooms are compared. Advantages and limitations of different methods are described. During the last few years the extent of microbiological sampling for environmental monitoring has increased in cleanrooms and clean zones. In spite of these increased efforts, results of environmental monitoring do not always give more reliable information on microbiological production safety than before. Some strategies for monitoring the cleanrooms, the clean zones and its processes are discussed. Experiences from application of the LR method (limitation of risk) concerning the choice of sampling points are also reported.

BSE: understanding the principles

David Tyrrell
Dr Tyrrell was previously chairman of the UK Spongiform Encephalopathy Advisory Committee

It is imperative that appropriate procedures are selected to guard against potential hazards due to BSE (bovine spongiform encephalopathy) in products intended for parenteral use. While guidelines have been produced by the licensing authorities, these often cannot be anticipated, or are vague in their method of application. This essay is written to outline the pertinent facts about the agent and to describe how the UK's response to the BSE epidemic was developed, as well as the main scientific facts on which this response was based. My hope is that under-standing these facts will demonstrate the principles, and understanding the principles will explain such guidance as is available and help to solve practical problems of detail.

Redefining the 'Sterility' of Sterile Products

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Users of parenteral products, in-dwelling medical devices and surgical dressings generally take the sterility of their product for granted and, in the

main, give very little consideration to the sterilisation process. The general assumption is that the manufacturers have adopted the most efficient and cost-effective methods of achieving sterility. But is this the case for all categories of sterile products? Moreover, do all pharmaceutical products which are labelled as ‘sterile’, require the same level of treatment? In this article we will examine the current specifications governing sterilisation processing within the pharmaceutical and medical devices industries, and demonstrate that in some instances the high standards set are unreasonable, not cost-effective, and may even lead to a reduction in the microbiological standards of some product categories.

Parenteral Society: the first 15 years

Gerry Prout
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Few people are as familiar as Gerry Prout with the origins of the Parenteral Society. One of its founder members, and first chairman, he and his wife June deserve much of the credit for the hard work involved in setting up and running what rapidly became a highly successful organisation. To mark this launch issue of the European Journal of Parenteral Sciences — the society’s latest achievement — what could be more appropriate than his account of how it all came into being?

VOLUME 1 NUMBER 2 1996

Contents

Experiences with Clean-In-Place Validation in a Multiproduct Biopharmaceutical Manufacturing Facility

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Validation of clean-in-place methods is a key activity in a multiproduct biopharmaceutical manufacturing facility. This paper describes performance qualification (validation) activities that have been used to verify that clean-in-

place methods for fermentation and purification equipment are effective in removing chemical residues (from cleaning agents), process residues (product or medium components, for example) and microbiological contamination. An overview of sampling methods, analytical methods and selection of acceptance criteria is described, together with a proposed performance qualification strategy that involves initial performance qualification, periodic requalification and on-going clean-in-place (CIP) monitoring.

Developments in Contamination Control and Cleanroom Standards: the work of ISO Technical Committee 209 on cleanrooms and associated controlled environments

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The years since 1992 have seen unprecedented international co-operation in the development of cleanroom and broader contamination control standards (CC Standards), under a programme scheduled to continue until mid-1977. The objective of this paper is to present a detailed update on the progress and development of the work, and on some of the key documents being developed within the International Standards Organisation's Technical Committee 209 group (ISO TC 209).

Removal of Asbestos Fibres by Microfiltration

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A research programme has been developed and carried out to evaluate the ability of micro-filtration membranes to remove non-viable particles, specifically asbestos fibres. Test membranes were challenged using polystyrene latex (PSL) sphere and asbestos fibre suspensions. By comparing upstream and downstream fibre concentration, reduction values for particle/fibre removal were derived. In a collaborative study, up to seven logarithmic reduction values (LRVs) were detected for 0.2 µm membranes. Owing to the highly sophisticated experimental methods required for such tests and the satisfactory removal efficiency of sterile filtration membranes, it

is advisable to restrict such testing to filter certification and/or process validation.

Preliminary Communication

Tests on the Colony Growth Properties of Sartorius Gelatin Membrane Filters After Exposure to Vapour Phase Hydrogen Peroxide

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Isolator cabinets with glove ports for work in a bacteria-free and low-particulate environment are being increasingly used in the pharmaceutical industry for handling test samples for the sterility test1 and for the production of pharmaceuticals2. According to Graham et al 3, decon-tam-ination of the cabinets can be achieved with vapour phase hydrogen peroxide, a reliable and environmentally friendly procedure4.

VOLUME 1 NUMBER 3 1996

Contents

Simulation of Airflows and Dispersion of Contaminants Through Doorways in a Suite of Cleanrooms

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In a suite of cleanrooms, many properties are interacting on contamination dispersion; the physical laws governing most of these processes are both well known and validated. However, they are interacting in a way that leads to large equation systems. With the growth in computer capacity, and

associated developments in numerical methods, it has now become possible to solve such equation systems. A new modular program system called IDA has been used for this investigation. The results show that, when temperature differences occur between cleanrooms with air changes and pressure differences that meet current Good Manufacturing Practice (GMP) requirements, there will be a risk of contamination ingress when a door is opened.

A System for Testing the Effectiveness of Microbiological Air Filters

SR Parks, AM Bennett, S Speight and JE Benbough
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A system is described which shows that Sartofluor hydrophobic filter cartridges used for sterilisation of air (supplied by Sartorius Ltd, Longmead Business Centre, Epsom, Surrey KT19 9QN, Catalogue number 518507 T9) were not adversely affected either after repeated heat sterilisation or after prolonged (seven days) exposure to humidified air. Using established microbial aerosol generation and air-sampling methods, no micro-organisms could be detected downstream of the filters when challenged by aerosolised Bacillus subtilis var niger spores (NCTC 10073) and MS-2 coliphages (NCIMB 10108). The titre reduction corresponded to over 4.2 × 1010 for the spores and over 3.8 × 109 for the coliphages when daily challenges were carried out over a week.

Validation of Enzymatic Inactivation of Cephalosporins Adhering to Environmental Monitoring Samples

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The aim of this study was to validate a method for the inactivation of cephalosporins which might interfere with hygiene monitoring performed in aseptic cephalosporin manufacturing areas. A model system consisting of media-filled contact plates, the cephalosporin cefotaxime sodium and the enzyme cephalosporinase (β-lactamase II) was used to optimise the enzyme concentrations. Data were also generated under normal operating conditions during the routine monitoring of a manufacturing area. The results indicate that an enzyme activity of 88 to 176 IU per litre of medium is required for valid monitoring results.

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Bioburden Testing of Recombinant Escherichia coli K-12 Fermentation Samples Using Bacteriophages T4 and P1

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In the production of biological products through the use of recombinant Escherichia coli, determining the non-E. coli bioburden load of fermentation samples and early-stage purification samples is often difficult. To allow for examination of such samples, a method employing the use of E. coli bacteriophages T4 and P1 has been developed. The method selectively reduces the background recombinant E. coli present to allow the detection of the samples' non-E. coli bioburden load. An evaluation of the method indicates that a 6-log reduction in background recombinant E. coli can be consistently achieved without affecting the viability of potential bacterial contaminants.

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VOLUME 1 NUMBER 4 1996

Contents

Validation of the drying procedure for freeze-dryer inlet filters after the water intrusion integrity test

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The demand for on-line sterilisation and integrity testing of sterilising-grade air filters used on freeze dryers and autoclaves1 has increased in the course of the last four years, following the development and introduction of technical solutions. The water intrusion test (WIT), based on the use of water as the testing medium, enables an on-line test of gas filters and has been correlated to the bacterial challenge test2. This testing procedure is

therefore proposed as a viable alternative to the existing diffusion test, which utilises an alcohol solution to wet the hydrophobic filters.

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Proposed modifications to the FDA's current Good Manufacturing Practice regulations

Gerry Prout
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Ever since June 1963, when the US Food and Drug Administration (FDA) first began publishing its current Good Manufacturing Practice (cGMP) regulations1, it has periodically introduced modifications to ensure that requirements continue to reflect technical and scientific progress. Major revisions were published in the Federal Register in 1971, 1978 and 1995.2,3,4

Philosophy and Validation Approach to Cleaning and Decontamination in Antibiotics Facilities

Wael Allan and Trevor Deeks*
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This paper describes a cleaning philosophy for different types of antibiotic facilities. The objective was to remove all traces of antibiotic from the internal and external surfaces of equipment and the surrounding areas, in order to prevent the contamination of any future product by the antibiotic in that facility. Because of the nature of the antibiotics involved (penicillin and cephalosporin), no detectable traces must remain. The paper considers both change of use and campaign manufacture.

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Environmental Pressures on the Disposal of Waste Packaging Materials: a commentary from the medical device industry viewpoint

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European estimates indicate that hospital waste represents only about 0.3 per cent of the volume of waste — over one billion tonnes in total — produced in the European Union (EU). Of this percentage, only a small proportion is packaging waste. However, all waste issues are very visible today and we in the medical device industry, like any other, must be seen to take a responsible role and, of course, comply with legislative requirements. The UK has never been a forerunner in national environmental legislation, and the EU requirements now emerging are largely based on existing German and Scandinavian national laws, which have been in place for some years.

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