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Content and Abstracts

Application of statistical models to action limits for media fill trials

Mauro Bernuzzi*, Nigel Halls* and Paola Raggi†
**Glaxo Wellcome Group Technical Services, Stockley Park, Uxbridge UK and *Glaxo Wellcome SpA, Verona, Italy*

The availability of drafts of a proposed ISO standard, currently identified as ISO/DIS 13408-1 and entitled Aseptic Processing of Health Care Products1, has created some considerable interest2,3,4 in the statistics applied to designing and evaluating results of media fill trials.

Life with the UK pharmaceutical isolator guidelines: a manufacturer's viewpoint

John Neiger
Chairman, Envair Ltd, Haslingden, UK

The UK document, Isolators for Pharmaceutical Applications, was published in 1994 by HMSO and is frequently referred to as ‘the UK pharmaceutical isolator guidelines’.1 The document was prepared as a result of an initiative by a group of regional quality control pharmacists working in the UK’s National Health Service (NHS), who assembled a working party comprising NHS pharmacists, the Medicines Control Agency, isolator manufacturers, and some representatives from the pharmaceutical industry.

Smart delivery of disease management Part 1: The scope for the integration of pharmaceuticals and diagnostics

David J Clarke and Harmesh S Aojula
School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK

Healthcare markets are undergoing significant long-term changes, driven by increased competition through low growth caused by the price constraints imposed by government purchasing agencies, as well as by decentralisation and a move towards evidence-based medicine. In order to maximise efficiency, the industry is consolidating. One result is fewer large healthcare companies, with small boutique or research firms providing technological innovations. Another result is that total disease management has become a focus of strategic innovation, leading to the integration of diagnostics and pharmaceuticals for particular diseases and the development of self-contained delivery packages which simplify ‘close-to-patient’ disease management. Such trends are heightened by the concurrent movement of resources away from acute to primary care and prevention.

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Studies on the theoretical basis of the water intrusion test (WIT)

Rolf Jaenchen1, Jörg Schubert1, Sima Jafari2 and Alison West2
Pall GmbH, Dreieich, Germany1 and Pall Europe Limited, Portsmouth, UK2

There is an increasing requirement to integrity test sterile air filters in situ. The water intrusion test (WIT) offers benefits over existing methods, but its scientific basis is not well understood. This study investigates what is being measured and provides data on the factors influencing the test. The role of evaporative flow when testing intact filters is clearly demonstrated and the effect of water quality and temperature quantified. This improved

understanding of the scientific basis of the test allows the factors influencing it to be controlled and enables a reliable correlation with bacterial challenge to be established.

Corresponding author: Dr Alison West, Pall Europe Limited, Walton Road, Portsmouth P061TD, UK.
Tel: (+ 44) 17053 303 563 fax: (+ 44) 17053 303 413.

Validation of a filter integrity test instrument

Paschal Baker and Trevor Deeks*
*Raytheon Engineers & Constructors UK and Boehringer Ingelheim UK Ltd (*while at Raytheon Engineers & Constructors UK)*

As part of a validation project for an aseptic filling operation, a Palltronic TruFlow filter integrity testing system was purchased and validated. This equipment is a recently introduced model, controlled by a PC computer, and is capable of performing the bubble point, forward flow and water intrusion tests. This paper describes the criteria for selection of the instrument, and the installation, operational and performance qualification of the equipment. It also provides recommendations for siting the equipment, and its maintenance.

Corresponding author: Paschal Baker, Validation Engineer, Raytheon Engineers & Constructors UK Ltd, CI Tower, St George's Square, High Street, New Malden, Surrey, KT3 4HH, UK. Tel: (+ 44) 181 388 0282, fax: (+ 44) 181 388 0253. E-mail: paschal_baker@ccgate.ueci.com

Investigations into the compatibility of teicoplanin with heparin

Carole Malcolmson1, Stephanie Zilka1, Jackie Saum1, Gary Moore2, Trevor Deeks1*
1Formerly at Hoechst Marion Roussel Research and Development Centre, Winnersh, Berkshire, UK, and 2Department of Haematology, Royal Hospitals NHS Trust, Whitechapel, London, UK

In contrast to the incompatibility observed between heparin and the glycopeptide vancomycin, this study indicates that no such incompatibility exists between the glycopeptide antibiotic teicoplanin (Targocid) and heparin. Analysis by high-performance liquid chromatography (HPLC) shows that no incompatibility is observed when teicoplanin and heparinised saline flushes are present in the same Hickman line catheter. Furthermore, HPLC analysis, microbiological assay and the in vitro determination of blood clotting time indicate that no incompatibility is seen when both teicoplanin

and heparin are present in 0.9% Sodium Chloride BP or 5% Dextrose Infusion BP fluids.

Corresponding author: Trevor Deeks, Boehringer Ingelheim Limited, Ellesfield Avenue, Bracknell, Berkshire RG12 8YS, UK.
Tel: (+ 44) 1344 741 112, fax: (+ 44) 1344 746 944.

Smart delivery of disease management Part 2: Advances in the integration of diagnostics into drug intervention

David J Clarke and Harmesh S Aojula
School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK

This paper examines advances in the delivery of disease management and drugs, particularly in the context of the strong and growing contribution of diagnostics. The development of targeted drugs utilising polymeric and liposomal drug carriers has made considerable use of diagnostic molecules — antibodies, enzymes, ligands, receptors and, more recently, DNA — for biorecognition. Less developed, but of increasing importance as the problems of delivery and biological stability are tackled, is the incorporation of the same molecules into self-regulating, bioresponsive drug delivery systems. Biology demonstrates many smart bioresponsive systems, with high degrees of targeting, amplification and bystander effects (the immune system is one example), whose use as biological materials or in synthetic mimics is also emerging. While information technology is showing early potential in improving drug usage, particularly in primary care, interest in simple drug administration and dosing devices and near-patient diagnostics is growing, providing the position for smart drug usage to develop.

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Ondina-EL as an alternative to DOP for the in-situ HEPA filter integrity test

Nigel Halls
Glaxo Wellcome Group Technical Services, Stockley Park West, Uxbridge, UK

In order to achieve the standards of cleanliness stipulated for facilities in which sterile pharmaceutical dosage forms are manufactured it is necessary for the supply of environmental air to be passed through HEPA (high-efficiency particulate air) filters. Manufacturers of HEPA filters certify their efficiency with respect to retention of particles of 0.3µm.1, 2 In Europe, the Eurovent system distinguishes five grades of HEPA filter, termed EU10 to EU14 on the basis of percentage retention efficiency (see Table 1). In the USA, HEPA filters are required to have minimum retention efficiencies of

99.97 per cent (EU12 and greater). It is not only essential that HEPA filters are efficient ‘ex factory’ with respect to the retention of particles, but also that their installation does not compromise their integrity through damage to the filter medium, or by permitting leakage of air between the medium and its frame, or between the frame and the ductwork of the air supply system. Assurance of the integrity of an installed filter system must be obtained via an in-situ integrity test, also referred to as the ‘leak test’ or the ‘DOP test’.

Correspondence: Nigel Halls, Quality and Technical Support Division, Glaxo Wellcome Group Technical Services, Stockley Park West, Uxbridge, Middx UB11 1BU, UK.
Tel: (+44) 181 990 2634, fax: (+44) 181 990 4313.

Compliance Guide: the FDA Final Rule on electronic records and electronic signatures

Philip A Rees
Independent Consultant, Validation and Compliance Services, Formello, Italy

This guide summarises the content and impact of the new Final Rule on Electronic Records and Signatures issued by the US Food and Drug Administration (FDA) in March, and effective from August 20, 1997. This addition to Chapter 21 of the Code of Federal Regulations (21 CFR Part 11) provides criteria for the FDA’s acceptance, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records, as the equivalent of paper records and handwritten signatures executed on paper. The use of electronic records as well as their submission to the FDA is voluntary. This paper presents comments on the regulations, together with an explanation of how they affect a pharmaceutical company’s research, development, production and distribution activities.

Correspondence: Philip A Rees is an independent consultant specialising in Good Manufacturing Practice and Good Automated Manufacturing Practice validation and compliance services. He can be contacted at via Mariano Marchicelli 2, 00060 Formello (Rm), Italy. Tel/fax: (+39) 6 9014 6033, mobile tel: (+39) 335 311 379, e-mail: p.rees@agora.stm.it.

Environmental monitoring and media fills in a blow-fill-seal facility

Pauline Johnstone

Microbiology Services Manager, Boehringer Ingelheim (UK) Limited, Bracknell, Berks, UK

For some years now, there has been considerable discussion regarding the minimum standards required for aseptic processing, and this has led to the appearance of a number of standards and technical dossiers on the subject.1-3 Most recently (1996), the European Commission published its revision of Annex 1 to the EU Guide to Good Manufacturing Practice which contains a number of requirements for aseptic processing and represents a raising of the standards.4 This annex is to be applauded for addressing an issue which concerns manufacturers as well as regulatory authorities. Interestingly, the revised environmental classification requirements and controls for blow-fill-seal facilities remain less stringent than those for classical filling of vials and ampoules. There are good technological reasons for this difference and blow-fill-seal technology represents a very 'safe' form of aseptic filling of aqueous solutions. This paper examines why the difference exists and demonstrates that a high degree of safety is nevertheless maintained.

Correspondence: Pauline Johnstone, Microbiology Services Manager, Boehringer Ingelheim (UK) Limited, Ellesfield Avenue, Bracknell, Berks RG12 8YS, UK.Tel: (+44) 1344 424 600, fax: (+44) 1344 741 444.

Commentary: TSEs and pharmaceuticals

Mike Murray
Technical and Environmental Affairs Executive, Science and Technology Department, Association of the British Pharmaceutical Industry, London, UK

The crisis over bovine spongiform encephalopathy (BSE) in the United Kingdom has caused a great deal of debate in the farming community since the late 1980s. Discussion on the potential transmission of the agent to humans has now extended to non-agricultural sectors – including medicinal products. The European Commission examined the question of medicinal products in 1996 and is reviewing its position in 1997. This commentary discusses the current situation, together with possible future actions.

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Analytical aspects of biopharmaceutical product development

John F Wright
Written while Director of Analytical Support and Development with Genetics Institute Inc., Andover, MA, USA

Historically, biopharmaceutical product development has been a race — to succeed and to get to market. Traditionally, it seems, biopharmaceutical companies, particularly those based on recombinant DNA technology, tend to be small start-up concerns spawned, if not directly from academia, then

with heavy academic input in terms of both ideas and personnel. They are generally funded, initially at least, with a limited supply of venture capital. With this background there is a strong drive towards getting rapidly into the clinic in order to show success and thus to keep the investment stream flowing. Subsequently, the race to get to the market continues in order to produce a return on those investments and often to beat a competitor to establish a market share. Within this overall, corporate race there is another race — that between process development and the supporting analytical development.

Correspondence: John F. Wright, Craich, Tough, Alford, Aberdeenshire AB33 8EN, UK. Tel: (+ 44) 19755 62584.

A comparative study of two floor-cover materials in control of foot- and wheel-borne contamination

Gerry Prout
Technical director, Kennet Bioservices Ltd, Stratton St Margaret, Wiltshire, UK

It is recognised that the interfaces between classified cleanrooms and less clean areas form a fragile barrier to the ingress of particles and micro-organisms into cleanrooms. In many cases, operators and materials are transferred into airlocks, subsequently entering the cleanroom via a simple ‘step-over’ bench barrier. The principles of quality assurance, in the manufacture of sterile medicinal products, include the requirement that particle and microbiological contamination levels should be minimised, both in the cleanroom and surrounding areas, to reduce the probability of such contamination entering the product.1,2 In this context, foot- and wheel-borne contamination represent two potential sources of viable and non-viable particles. This paper describes the relative reduction in these two potential sources achieved by two different, commonly used types of floor cover. Polymeric floor cover was found to be more effective in the reduction of foot- and wheel-borne contamination, over a wide range of particle levels, than was the surface of a ‘peel-off’ or ‘tacky’ mat.

Correspondence: Gerry Prout, Technical Director, Kennet Bioservices Ltd, Parkside, Swindon Road, Stratton St Margaret, Wiltshire SN3 4PY, UK, tel: +44 (0) 1793 831 595, fax: + 44 1793 831 112, mobile: + 44 410228 377, e-mail: kennetbioservices@prout.demon.co.uk

Use of the HACCP concept for the risk analysis of pharmaceutical manufacturing processes

Dr Michael Jahnke
Quality Assurance/Microbiology Department, Pharma Hameln GmbH

In order to guarantee the manufacture of consistently high-quality medicinal products for human use, it is absolutely essential that flawlessly clean conditions are maintained through the strict observance of hygiene rules. The purpose of such rules is to ensure that measures are taken to protect such products from any type of contamination during the manufacturing process. The user of the product is thereby shielded from risks to health through chemical or biological impurities, and so is more likely to accept the preparation, and the product is protected from any bioburden.

Correspondence: Dr Michael Jahnke, Quality Assurance/Microbiology Department, Pharma Hameln GmbH, Langes Feld 13, D-31789 Hameln, Germany, tel: + 49 5151 581 283, fax: + 49 5151 581 258.

Blow-fill-seal technology for aseptic production

Dr Martin Haerer and Urs Lichtenstein*
*Holopack Verpackungstechnik GmbH, Sulzbach-Laufen, Germany and *rommelag ag, Buchs, Switzerland*

In the revised EU GMP Annex on the manufacture of sterile medicinal products1 a separate paragraph is dedicated to blow-fill-seal (BFS) technology. It states that: ‘blow-fill-seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used.’ One type of blow-fill-seal equipment which has been available for a number of years was purpose-built to reduce particle levels in the machine and in its environment, through a new technology known as ‘white/dark execution’.

Short communication
The ChemScan system: a new method for rapid microbiological testing of water

Günter Wallner*, Dirk Tillmann*, Klaus Haberer*, Philippe Cornet** and Jean-Louis Drocourt**

** Hoechst Marion Roussel, Quality Operations Microbiology, Frankfurt, Germany*
*** Chemunex SA, Paris, France*

The ChemScan system is a new analytical method for the rapid detection and enumeration of viable micro-organisms. It is based on direct fluorescent labelling of microbial cells on membrane filters and subsequent detection by a laser scanner. First results of comparative studies on diluted cultures and on water samples show that this system is much faster (total testing time less than two hours) than the standard plate count methods and at least as sensitive.

Correspondence: Dr Günter Wallner, Hoechst Marion Roussel, Quality Operations, Microbiology, H785, D-65926 Frankfurt/Main, Germany, tel: (+49) 69 305 7426, fax: (+49) 69 305 17374, e-mail wallner@hmrag.com.