

Contents

Editorial: On requirements, guidance and advice	1
Commentary: TSE – yet another update! Mike Murray	2
The detection of residual air in steam autoclaves Robert T. Newton	5
Commentary: Bringing quality assurance and validation into research and development – points to consider Carmen M. Wagner	12
Conference overview: French without tears	19
Conference overview: The big issues	20
ESPC briefing	23
For your bookshelf	23
Dates for your diary	26
Index for Volume 3	28

Instructions for authors in this issue

Contents & Abstracts

Commentary: TSE – yet another update!

Mike Murray

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

The play *The Mousetrap* has run in London's West End for about 40 years – and it seems the TSE debate could have an equally long run.

Correspondence: Mike Murray, ABPI, 12 Whitehall, London SW1A 2DY, UK.
Tel: (+44) 171 747 1421, fax: (+44) 171 747 1413.

The detection of residual air in steam autoclaves

Robert T. Newton
Managing Director, MMM Group, Harrogate, UK

The proper delivery of a regulatory-compliant porous loads steriliser – a necessity in all sectors of the UK healthcare and pharmaceutical industries – requires careful attention to how air detectors are calibrated and their performance interpreted. This paper argues the need for a more scientific approach to the requirement to have knowledge of what the gas contents of the autoclave drain line are at all stages of the cycle. It also introduces the concepts behind a radically new type of air detector, the IPC (In-process Control).

Correspondence: Robert T. Newton, Managing Director, MMM Group, 9 Cardale Park, Beckwith Head Road, Harrogate, North Yorkshire HG3 1RY, UK. Tel: (+ 44) 1423 523 300, fax: (+ 44) 1423 52820, e-mail: robert@pharma.demon.co.uk

Commentary: Bringing quality assurance and validation into research and development — points to consider

Dr Carmen M. Wagner
Director, Quality Assurance/Quality Control, Wyeth-Lederle Vaccines and Pediatrics, Sanford, North Carolina, USA

Vaccines development requires years of development and testing and calls for the integration of technical and administrative team work, to ensure the quickest path from discovery to commercialisation. Two of the key departments involved are quality assurance (QA) and validation. The distinct functions of these groups complement each other. QA is responsible for determining the readiness of a product for clinical release or commercialisation, and decides on product disposition. Validation is the discipline responsible for the effective performance of the equipment, facility and the process. Validation helps ensure that quality is built into these components of the product system. In this paper, the word 'quality' is inclusive of quality assurance and validation.

Correspondence: Carmen M. Wagner, PhD, Wyeth-Lederle Vaccines and Pediatrics, 4300 Oak Park, Sanford, NC 27330, USA. Tel: (+ 1) 919 775 7100 x 4306, fax: (+ 1) 919 774 1142.

Conference overview: French without tears

Is engagement in the learning process compatible with good weather, a beautiful seashore and the cries of seagulls? Yes, writes Didier Meyer, if you attended the 11th A3P Congress held from October 14–16 at the Palais des Congrès d’Arcachon (near Bordeaux in south-west France), with its state-of-the-art amphitheatre and audiovisual facilities.

Contents

Editorial:	31
Developing regulatory authority requirements for barrier and isolator technologies Andrew Bill	32
Protecting operators and the environment from toxic or potent APIs John Crawley	37
Use of isolators in a specials manufacturing environment Susan Browne, John Horry, Robert Lund, Alan Mills	43
Practical validation and monitoring of isolators used for sterility testing Allan Whipple	49
The use of isolators for cytotoxic drug handling in hospital pharmacies Graham Sewell	55
Microbiological considerations in the operation of isolators for aseptic pharmaceutical manufacture Andrew Lewis and Sharon Johnson	60
Integrating isolators with automatic filling lines Gianfranco Salmi and Andrewa Cicconetti	67
Validation of an open exit in a sterile pressurised enclosure Dave Adams	73
For your bookshelf	78
Dates for your diary	82

Instructions for authors in this issue

Contents & Abstracts

Developing regulatory authority requirements for barrier and isolator technologies

Andrew Bill

Senior Medicines Inspector, UK Medicines Control Agency

This article describes how establishing the regulatory guidelines for isolator and barrier technologies means going back to basics – and back to the future. The emphasis is on the use of these technologies to control the microbiological condition of environments used in the production of sterile medicines. Comments mainly relate to aseptic processing, although the technologies may also be used for products that will be terminally sterilised. The use of these technologies for containment to protect the operators and external environment is not specifically addressed, but in some circumstances may be of considerable importance. Unless otherwise indicated, the opinions expressed are personal and do not necessarily represent the official policy of the Medicines Control Agency (MCA) or any other regulatory body.

Correspondence: Andrew Bill, MCA Inspector, Second Floor, Prudential House, 28-40 Blossom Street, York YO24 1GJ, UK. Tel: (+ 44) 1904 610 556, fax: (+ 44) 1904 625 430.

Protecting operators and the environment from toxic or potent APIs

Dr John E Crawley

Technical Team Leader, SmithKline Beecham Pharmaceuticals, Worthing, West Sussex, UK

As the improved understanding of target active sites drives the design of lead compounds in research and development, the pharmaceutical industry is increasingly seeing more potent medicines. This trend can have a beneficial effect for the primary manufacturing side of the business, in that existing plant capacities can often meet the usually smaller demands of these potent compounds. However, the handling of such compounds in bulk represents a technical challenge to the operating team and equipment. For toxic, high-volume products, of course, this issue can represent even more of a challenge, with perhaps tonne quantities of hazardous material being handled.

Correspondence: Dr John E Crawley, Technical Team Leader, SmithKline Beecham Pharmaceuticals, Worthing, West Sussex BN14 8QH, UK. Tel: (+ 44) 1903 822 816, fax: (+ 44) 1903 822 057

Use of isolators in a specials manufacturing environment

Susan Browne, John Horry, Robert Lund, Alan Mills
Boots Contract Manufacturing, Nottingham, UK

The sterility assurance of small-scale aseptic processing can be enhanced by the use of carefully designed, validated and operated isolators. This article emphasises that correct aseptic technique should not be replaced by the isolator technology; rather, the technology should be used to enhance it. There are a number of problems associated with the use of isolators, not least the ergonomic issues for operators. Some of these problems are discussed, and various solutions suggested.

Corresponding author: John Horry, BCM Specials, Boots Contract Manufacturing, Nottingham NG2 3AA, UK. Tel: (+ 44) 115 968 6676, fax: (+44) 115 959 1098.

Practical validation and monitoring of isolators used for sterility testing

Alan J. Whipple
Microbiology Manager (International Actives Supply), Glaxo Wellcome Operations, Cumbria, UK

This paper examines key considerations in the validation and monitoring of sterility-test isolator systems, and emphasises the need for a thorough definition of requirements during the design qualification phase of validation. It also highlights the importance of performance qualification and describes specific techniques for proving that sterile conditions can be obtained without adverse effects on the sterility test. The routine monitoring procedures recommended assure maintenance of sterile conditions without themselves compromising the isolator environment.

Correspondence: Alan J. Whipple, Microbiology Manager, International Actives Supply, Glaxo Wellcome Operations, North Lonsdale Road, Ulverston, Cumbria LA12 9DR, UK. Tel: (+ 44) 1229 482 370, fax: (+ 44) 1229 482 004, e-mail: ajw90885@glaxowellcome.co.uk

The use of isolators for cytotoxic drug handling in hospital pharmacies

Graham J Sewell

Professor of Clinical Pharmacy/Pharmacy Practice, University of Bath

Many issues relating to isolator use in hospital pharmacies are under debate, including the quality of the background environment, sanitisation of materials transferred into isolators, the use of positive or negative pressure isolators for cytotoxics, ergonomics and gaseous sterilisation. However, continuing improvement in isolator design, isolator monitoring and the understanding of isolator technology means that the use of these devices is now well established in the UK and is becoming increasingly widespread throughout mainland Europe.

Correspondence: Graham J Sewell, Professor of Clinical Pharmacy/ Pharmacy Practice, Department of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, UK. Tel: (+ 44) 1225 323 782, fax: (+ 44) 1225 826 114.

Microbiological considerations in the operation of isolators for aseptic pharmaceutical manufacture

Andrew Lewis and Sharon Johnson

Worldwide Industrial Operations, Rhône-Poulenc Rorer, Dagenham, Essex, UK

The microbiological aspects of design, qualification and monitoring discussed in this paper are based on practical experience gained since 1993 of operating isolators for the aseptic manufacture of sterile products. Overall, requirements must mimic those applicable to the conventional cleanroom. However, the inherent threats to sterility assurance which exist with isolator operation will force more demanding programmes, in terms of both scope and time, at each step from design through to routine maintenance and requalification.

Corresponding author: Dr Andrew Lewis, WIO Industrialisation, Rhône-Poulenc Rorer, Rainham Road South, Dagenham, Essex RM10 7XS, UK.

Integrating isolators with automatic filling lines

Gianfranco Salmi and Andrea Cicconetti

R&D Department, IMA Liquid & Powder Filling Business Unit, Bologna, Italy

There is an increasing trend for the pharmaceutical industry to use isolator technology coupled with automatic filling systems, in order to minimise direct human contact with the process. The improved product handling conferred by such systems means that the risk of microbiological and particulate contamination is reduced, thus enhancing the assurance of product sterility, and it also has the potential to protect the operator from toxic or hazardous compounds. The operator never enters the processing area directly, since all the manual interventions are carried out by using special gloves fixed to the external walls of the isolator enclosure.

Corresponding author: Gianfranco Salmi, R&D Department, Liquid & Powder Filling Business Unit, IMA, via Emilia 428-442, Ozzano Emilia, Bologna 40064, Italy. Tel: (+39) 051 6514 825, fax: (+39) 051 6514 821, e-mail: rd.fillingute@ima.it

Validation of an open exit in a sterile, pressurised enclosure

Dave Adams

*Senior Engineer, IV Systems Division, Baxter Healthcare Corporation,
Round Lake, Illinois, USA*

In order for positive pressure, barrier isolation filling operations to approach true continuous or semi-batch operation, an open exit must be provided for the product flow. Transfer of materials is the biggest challenge for high-speed line applications, which manufacturers continue to address with 'mouse holes' or 'open air locks' (doors)¹. An exit such as this is in use at Baxter Healthcare's haemoglobin therapeutics plant, and this paper describes how it was validated. The product is aseptically filled into flexible solution bags in a Class 100 isolator, EC Grade A, M 3.5, and dropped through an open-exit bag discharge into a Class 100,000 room.

Correspondence: Dave Adams, Baxter Healthcare Corporation, Rt. 120 & Wilson Rd, Round Lake, IL 60073, USA. Tel: (+ 1) 847 270 4575, fax: (+ 1) 847 270 2983, e-mail: adamsda@baxter.com

Contents

Editorial: Packaging assurance	85
A review of BSE and its inactivation AJM Garland	86
More about BSE testing	93
A general approach to the validation of sterilising filtration used in aseptic processing S Docksey, J-M Cappia and D Rabine	95
Recent developments in the European regulation of ophthalmic, parenteral and other sterile products BR Matthews	103
Points to consider: Airborne microbial effect of in-leakage in a negative isolator John Neiger	111
The Great Isolator Debate	113
ESPC briefing	114
Dates for your diary	115
Letter to the editor	118

Instructions for authors in Vol 4. No. 2

Contents & Abstracts

A review of BSE and its inactivation

AJM Garland, BVMS, PhD, CBiol, MRCVS
International veterinary and medical consultant

This paper gives a brief review of the inactivation of agents causing transmissible degenerative encephalopathies (TDEs), in the context of pharmaceutical and biological manufacture. It briefly summarises the history

of bovine spongiform encephalopathy (BSE) and selectively reviews the literature relating to the inactivation of the agents causing TDEs. It makes particular reference to BSE and scrapie, and also to materials and equipment commonly used in the manufacture of biological and pharmaceutical products.

Correspondence: AJM Garland, Collingwood, Dawney Hill, Pirbright, Surrey GU24 0JB, UK. Tel: (+44) 1483 47 3476, fax: (+44) 1483 480 023, e-mail: Tony.Garland@btinternet.com

A general approach to the validation of sterilising filtration used in aseptic processing

Steve Docksey (General Manager, Europe), Jean-Marc Cappia (Aseptic Processing Marketing Manager) and Denis Rabine (European Market Manager)

Millipore SA, Molsheim, France

This paper proposes a general validation master plan for sterilising filtration as used in aseptic processing, and lists the different types of testing needed to meet current US Food and Drug Administration (FDA) and European Union (EU) regulatory requirements.

Corresponding author: Jean-Marc Cappia, Aseptic Processing Marketing Manager, Millipore SA, 39 Route Industrielle de la Hardt, BP 116, 67120 Molsheim, France. Tel: (+ 33) 3 88 38 90 00, fax: (+ 33) 3 88 38 91 93, e-mail: jean-marc_cappia@millipore.com

Recent developments in the European regulation of ophthalmic, parenteral and other sterile products

Brian R Matthews, BPharm, PhD, MRPharmS, MBIRA
Director, EC Registration, Alcon Laboratories (UK) Ltd, Hemel Hempstead, UK

This paper outlines recent changes to the guidance available on the manufacture of sterile medicinal products from a number of regulatory sources. Taken together with the regulatory experience over the last few months of a number of companies in the ophthalmic pharmaceutical sector, covering a number of products, these changes suggest that there is a considerable shift in the attitude of regulatory authorities to the use of manufacturing processes other than terminal sterilisation. Some of the companies' experiences will be briefly described.

Correspondence: Brian R Matthews, Director, EC Registration, Alcon Laboratories (UK) Ltd, Hemel Hempstead HP2 7UD, UK. Tel: (+ 44) 1442 341 234, fax: (+ 44) 1442 341 280, e-mail: lt09@dial.pipex.com

Points to consider: Airborne microbial effect of in-leakage in a negative isolator

John Neiger

Chairman, Envair Ltd, Haslingden, Lancashire, UK

This paper sets out theoretical calculations which relate the level of contamination that could arise in a negative isolator directly to the results of the pressure decay test on that isolator and the quality of air in the background environment. Similar theoretical calculations are set out for a glove/sleeve leak test. Both indicate a low risk of significant contamination from an in-leakage provided the isolator is operating within specification. Calculations, as worked through in this paper, can be applied to different isolators and the results used for the purpose of carrying out risk assessments.

Correspondence: John Neiger, Chairman, Envair Ltd, York Avenue, Haslingden, Rossendale, Lancashire BB4 4HX, UK. Tel: (+ 44) 1706 228 416, fax: (+ 44) 1706 229 577, e-mail: jneiger@envair.co.uk

Contents

Editorial: Never mind the width	119
Use and comparison of impact microbial air samplers in microbiological environmental monitoring Michael Jahnke	120
Revised Annex 1 of the EC GMP Guide: VFA comments and Interpretation L Gail, K. Haberer, W Huhn et al	127
Evaluation of the applications of a system for real-time microbial analysis of pharmaceutical water systems G Gapp, S Guyomard P Nabet and J Scouvert	131
Injectable lipid emulsions obtained through sonication J Medina, C Faulí and A del Pozo	138
Points to consider: Isolator venting using membrane filters MW Jornitz	143
Letters	148
Dates for your diary	154
Book Reviews	157

Instructions for authors in Vol 4. No. 2

Contents & Abstracts

Use and comparison of impact microbial air samplers in microbiological environmental monitoring

Dr Michael Jahnke
Head of Microbiology, Pharma Hameln GmbH, Hameln, Germany

The detection efficiency of three impaction-based microbial air samplers (RCS Plus, MAirT and KS 101) was compared in a validation study of

hygiene control (environmental monitoring) in the pharmaceutical industry. The susceptibility to drying-out of the culture media systems used in the three devices (nutrient agar cassettes, nutrient agar foils and agar plates) was also investigated. The effects of the impaction systems on the test environment were analysed by particle counts.

Correspondence: Dr Michael Jahnke, Head of Microbiology, Quality Assurance/Microbiology Department, Pharma Hameln GmbH, Langes Feld 13, Hameln, Germany. Tel: (+ 49) 5151 581 283, fax: (+ 49) 5151 581 258, e-mail: m.jahnke@pharma-hameln.de

Revised Annex 1 of the EC GMP Guide: VFA comments and interpretation

L.Gail, K.Haberer, W.Huhn, B.Käppel, D.Krüger, U.Lichtenberg, M.Limbert, C.Marg, P.Ober, H.P.Riniker, G.Schönberger, H.Schulz, H.Seyfarth, E.Sirch, S.Throm

Aventis Research & Technologies GmbH & Co KG (formerly Hoechst Research & Technology Deutschland), Frankfurt am Main, Germany

This paper represents a considered criticism of revised Annex 1 of the EC GMP Guide: Manufacture of Sterile Medicinal Products¹, put together by the VFA (the German Association of Research-based Pharmaceutical Manufacturers). It comprises a number of comments aimed at facilitating the interpretation and practical application of the Annex. Its conclusions have been accepted by the VFA subgroup, Microbiological/Technical Quality Assurance, and the VFA expert group, Production, Quality and Environment.

Corresponding author: Dr Lothar Gail, Aventis Research & Technologies GmbH & Co KG, Industriepark Höchst, Gebäude G 810, D-65926 Frankfurt am Main, Germany. Tel: (+ 49) 69 305 3429, fax: (+ 49) 69 305 82312, mobile: (+ 49) 172 683 1190, e-mail: gail@aventis.com, web: <http://www.aventis.com>

Evaluation of the applications of a system for real-time microbial analysis of pharmaceutical water systems

Dr Gunter Gapp, Dr Sylvie Guyomard, Dr Pascale Nabet, Dr Jean Scouvert
Dr Gapp is Quality Assurance Microbiology, Biochemie GmbH, Austria; Dr Guyomard, Section Manager, Rhône-Poulenc Rorer, France; Dr Nabet, Head of Microbiology Control, Hoechst Marion Roussel, France; Dr Scouvert, Head of Quality Control, UCB Pharma, Belgium

As the most widely used ingredient in drug manufacture, and the most extensively used solvent in equipment and system cleaning cycles, the production of purified water is central to nearly all pharmaceutical manufacturing plants. From both a regulatory and financial point of view, ensuring the quality of pharmaceutical water is, therefore, absolutely crucial.

Co-ordinating/corresponding author: David Jones, Director of Quality Assurance and Regulatory Issues, Chemunex SA, Immeuble Paryseine, 3 Allée de la Seine, 94854 Ivry-sur-Seine, Cedex, France. Tel: (+ 33) 149 59 20 00, fax: (+ 33) 149 59 20 01, e-mail: david-jones.chemunex@worldnet.fr

Injectable lipid emulsions obtained through sonication

J. Medina, C. Faulí, A. del Pozo
Pharmacy Department, University of Barcelona, Spain

This paper concerns the design of an experimental approach to possible formulations for injectable lipid emulsions, using sonication (by ultrasound probe) to achieve emulsification-homogenisation.

Corresponding author: Profesor Alfonso del Pozo, Unitat de Farmàcia Galénica, Facultat de Farmàcia, Plaza Pius XII s/n. 08028, Barcelona, España. Tel: (+ 34) 9 3402 4547, fax: (+ 34) 9 3403 5936, e-mail: APOZO@far.ub.es

Points to consider: Isolator venting using membrane filters

Maik W. Jornitz
Director of Product Management, Sartorius AG, Göttingen, Germany

Isolators are commonly vented by HEPA (high-efficiency particulate air) filters to separate particles and airborne microbial contamination; the filters also constitute the final barrier between the surrounding environment and atmosphere.^{1, 2} Filters should be integrity-tested on a regular basis, to ensure that they are fault-free. However, the integrity test used for HEPA filters is often an oil-based aerosol challenge test, which requires downstream manipulation from inside the isolator, can produce contamination of the filter matrix, and usually lacks sufficiently high sensitivity.³ This paper therefore proposes the use of membrane sterilising-grade filters, which can be reliably integrity-tested on a batch-to-batch basis and in a user-friendly way.

Correspondence: Maik W. Jornitz, Director of Product Management,
Sartorius AG, D-37070 Göttingen, Germany. Tel: (+ 49) 551 308 680, fax: (+
49) 551 308 918, e-mail: MWJornitz@compuserve.com