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Commentary: TSE – yet another update!

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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.

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The detection of residual air in steam autoclaves

Robert T. Newton
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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).

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

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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.

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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.

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Developing regulatory authority requirements for barrier and isolator technologies

Andrew Bill
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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.

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Protecting operators and the environment from toxic or potent APIs

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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.

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Use of isolators in a specials manufacturing environment

Susan Browne, John Horry, Robert Lund, Alan Mills
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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.

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Practical validation and monitoring of isolators used for sterility testing

Alan J.Whipple
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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.

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The use of isolators for cytotoxic drug handling in hospital pharmacies

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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.

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Microbiological considerations in the operation of isolators for aseptic pharmaceutical manufacture

Andrew Lewis and Sharon Johnson
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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.

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Integrating isolators with automatic filling lines

Gianfranco Salmi and Andrea Cicconetti

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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.

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Validation of an open exit in a sterile, pressurised enclosure

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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.

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A review of BSE and its inactivation

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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.

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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)
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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.

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

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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.

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

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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.

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

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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.

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

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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.

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

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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.

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Injectable lipid emulsions obtained through sonication

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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.

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Points to consider: Isolator venting using membrane filters

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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.

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