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Routes of contamination: aseptic processing case studies

Richard L Friedman
Center for Drug Evaluation & Research, Office of Compliance, Division of Manufacturing & Product Quality

This paper summarises parenteral drug contamination case studies presented at industry conferences and an FDA advisory committee meeting in the period of 2000-2004. CGMP deficiencies associated with each non-sterility event are discussed.

Key words: Aseptic processing; Process design

Corresponding author: Richard L. Friedman; Tel: +1 301 827 9031; email: friedmanr@cder.fda.gov

Examination of the optimal cultural conditions for the microbiological analysis of a cold demineralised water system in a pharmaceutical manufacturing facility

Tim Sandle and Kerry Skinner
Microbiologists, Bio Products Laboratory, Elstree, Hertfordshire, UK

This paper outlines a microbiological study of a demineralised water system in a pharmaceutical manufacturing unit. The study involved performing the total viable aerobic count on 100 water samples using three different culture media: Plate Count Agar (as recommended by the APHA); R2A (as recommended by supplement 4.2 of the Ph Eur) and tryptone soya agar (as recommended by previous editions of the Ph Eur). The study found that TSA was the least suitable medium for the testing of a demineralised water system; and that the results for R2A and PCA were statistically similar

Key words: Microbiological culture media; Total viable aerobic count; Pharmaceutical water

Corresponding author: Tim Sandle, Microbiologist, Bio Products Laboratory, Dagger Lane, Elstree, Herts, WD6 3BX. UK.
email: tim.sandle@bpl.co.uk (work); timsandle@aol.com (home). telephone: 0208-258-2483; fax 0208-258-2608

Developments in nanotechnology and nanomaterials in pharmaceutical science

David Carey
Advanced Technology Institute, University of Surrey, Guildford, UK

An understanding of the diverse nature of nanotechnology and the advantageous properties of nanomaterials is gaining an appreciation across a whole range of disciplines. In this paper the role of nanotechnology as an enabling technology, and the characteristics of nanomaterials in general and to drug delivery systems in particular, will be presented. A brief discussion of some of the more common tools of nanotechnology leads to a description of nanopatterning using dip-pen nanolithography. Some of the important properties and applications of a range of ‘bottom up’ produced nanomaterials including functionalised carbon nanotubes and dendrimers are highlighted as well as the use of quantum dots which can be used as fluorescence biomedical tags.

Key words: Nanotechnology; nanomaterials; drug delivery systems

Corresponding author: David Carey, Lecturer and EPSRC Advanced Research Fellow, Nanoelectronics Centre, Advanced Technology Institute, School of Electronics and Physical Sciences, University of Surrey, Guildford, GU2 7XH; email: David.Carey@surrey.ac.uk

GMP Training in the pharmaceutical Industry – a continuous challenge

Dr. Manuela Scholz* and Dr. Michael Jahnke**
* *Quality Control, Procter & Gamble Pharmaceuticals – Germany GmbH*
** *Quality Assurance, Wülfing Pharma GmbH, Grunau, Germany*

GMP training is an official, major requirement. Proof of adequate staff expertise and qualifications must be provided. Training needs have to be defined, internal and external training implemented and effective training has to be organised.
The training program content must be stipulated and the type of training available adapted in line with staff and company requirements.

GMP-Schulungen im pharmazeutischen Umfeld stellen eine behördliche Anforderung dar. Es ist der Nachweis einer ausreichenden fachlichen Qualifikation des Personals im Pharmabetrieb zu erbringen. Hierzu ist der Schulungsbedarf zu ermitteln, geeignete interne oder externe Schulungsmassnahmen durchzuführen und ein effektives Schulungssystem zur Organisation der Schulungsmassnahmen zu etablieren.
Die Inhalte der Schulungsmassnahmen sind dabei zu definieren und die Form der Schulung den Bedürfnissen anzupassen.

Key words: GMP training; Training requirements; Internal and external training;
Training qualification; Monitoring; Training system

Corresponding author: Dr. Michael Jahnke, Wülfing Pharma GmbH, Qualitätssicherung, Bethelner Landstraße 18, D-31028 Gronau.
email: michael.jahnke@wuelfing.de

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Facility design considerations for large scale production of biologicals:

GMP and containment synergies

Vibeke Halkjær-Knudsen
Director Viral Vaccines, Denmark

The biosafety level for Polio vaccine production is being upgraded as poliomyelitis is close to being an eradicated disease. This necessitates upgrading IPV (Inactivated Polio Vaccine) facilities around the world to a higher and more stringent biosafety level. Merging GMP and high containment regulations is necessary, and the subsequent decision about either building a new facility or upgrading the existing must be made.

Basically biosafety guidelines and GMP rules support and reinforce each other, but in some cases they contradict. When working with high-risk agents, totally new vaccines or soon eradicated agents, containment must be achieved, but product safety must not be compromised. Risk assessments should be the main tool to evaluate contradicting recommendations seen from product-GMP, biocontainment, environmental and personal safety points of view.

Key words: GMP, biosafety, risk analysis, facility design, large scale production, decontamination, fumigation, IPV, poliomyelitis, polio, high containment.

Corresponding author: Vibeke Hakjær-Knudsen PhD, Director Department of Viral Vaccines, Statens Serum Institute, Artillerivej 5,
DK 2300 S; Tel: +45 32 68 38 33; Fax: +45 32 68 38 72; Email: vhk@ssi.dk

Collection efficiency of microbial methods used to monitor cleanrooms

W Whyte
University of Glasgow

Microbiological sampling methods used in pharmaceutical cleanrooms should efficiently collect and count microorganisms. Methods are described in this paper that allow collection efficiencies to be determined and maximised, and comparisons to be made between sampling methods.

Key words: microorganisms, collection efficiency, surface sampling, air sampling,
monitoring, cleanrooms

Corresponding author: W Whyte, James Watt Building, University of Glasgow, Glasgow, G12 8QQ, UK. Telephone: +44(0) 141 330 3699, email: whytew@mech.gla.ac.uk.

Scintigraphic imaging for inhaled drug delivery: much more than pretty pictures?

Paul Clewlow and Steve Newman
Pharmaceutical Profiles Group Ltd, Nottingham, UK

Drug delivery to the lungs may be assessed in vivo by scintigraphic imaging, but this is sometimes dismissed as an exercise in obtaining “pretty pictures” of the lungs. In fact, scintigraphic imaging is a quantitative method which allows drug deposition to be determined in either two or three dimensions. The three-dimensional imaging technique of single photon emission computed tomography (SPECT) provides more precise information about the distribution within the lungs than two-dimensional imaging. Scintigraphic data may be obtained concurrently with pharmacokinetic and/or pharmacodynamic data, which allows the relationship between deposition, absorption and efficacy of inhaled drugs to be explored in depth.

Key words: gamma scintigraphy, single photon emission computed tomography (SPECT), pharmacokinetics, magnetic resonance imaging (MRI)

Corresponding author: Dr S P Newman, Scientific Advisor, Pharmaceutical Profiles Group Ltd., Mere Way, Ruddington Fields, Nottingham NG11 6JS
email: steve.newman@pharmprofiles.co.uk

Photochemical stability problems associated with parenteral preparations – An overview

Solveig Kristensen
Associate Professor, School of Pharmacy, Department of Pharmaceutics, University of Oslo, Norway

Parenteral dosage forms represent a group of pharmaceutical products that are especially susceptible to degradation by photochemical reactions. The photochemical instability can be ascribed to optical transparency of these preparations, formulation properties that enhance (photo)chemical reactions, frequent light exposure during storage and administration, and reconstitution prior to administration that may change drug photostability. The influence of in use conditions on photochemical stability is especially important for parenterals, but the aspect is not included in the ICH guidelines for photochemical stability testing of drugs. Thus photoprotection of pharmaceutical preparations is generally required during storage and administration, unless photostability under the actual conditions can be documented. These aspects are presented and discussed in this article, with the aim to introduce the reader to general problems associated with photochemical stability of parenteral drug products.

Key words: photoprotection, drug formulation, reconstitution, absorption properties, degradation kinetics, degradation products, experimental conditions, container transparency

Corresponding author: Solveig Kristensen PhD, Associate Professor, School of Pharmacy, Department of Pharmaceutics, University of Oslo, P.O.Box 1068, Blindern, N-0316 Oslo, NORWAY. Phone: +47 22 85 42 18; Fax: +47 22 85 44 02; email: solveig.kristensen@farmasi.uio.no

Containment and new trends

Gary Heath
Heath Containment Solutions Ltd

The pharmaceutical industry is working rapidly towards replacing Personal Protection Equipment (PPE) with Containment of Process, as per the COSHH 2002 Hierarchy of Control. Reducing Operator Exposure Limits (OELs) to a minimum has resulted in new market trends and innovations to meet the required criteria.

Key words: OEL, WEL, COSHH 2002 Hierarchy of Control, SMEPAC guideline, OEB

Corresponding author: Gary Heath, Heath Containment Solutions Ltd, GEA Buck Valve UK. PO Box 8554, Tamworth, Staffs B77 5FZ;
Tel: + 44 1827 251126; Fax: + 44 1827 288024; Mobile: + 44 7798 766600
www.buckvalve.de; www.envair.co.uk

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Cleaning investigations to reduce the risk of prion contamination on manufacturing surfaces and materials

G McDonnell,1 G Fichet3, K Antloga1, H Kaiser2, M Bernardo2, C Dehen3, C Duval3, E Comoy3, J-P Deslys3.
1STERIS Corporation, 5960 Heisley Road, Mentor, OH 44060, USA
2STERIS Corporation, 7405 Page Avenue, St. Louis, MO 63133
3CEA/DSV/DRM/GIDTIP, 18 Route du Panorama, 92265 Fontenay-aux-Roses, France

Prions are proteinaceous infectious agents which have been shown to be transmissible in tissues of human/animal origin and their derivatives, and on surfaces. The potential for contamination of surfaces and materials with

prions poses a unique consideration for control in pharmaceutical or particularly biopharmaceutical manufacturing facilities. Risk analysis has highlighted two key areas to reduce this concern: controlled sourcing and validated decontamination. For decontamination of surfaces, the most widely used process includes the handling and application of high concentrations of sodium hydroxide, which can be aggressive on surfaces and presents significant safety risks to a manufacturing facility. This report discusses the issue of alternative prion decontamination methods to reduce risks of cross-contamination. Research into the cleaning of surfaces has identified some surprises, with the identification and verification of novel cleaning technologies for prion decontamination and inactivation.

Key words: prions, decontamination, cleaning, TSE

Corresponding author: Dr. Gerald McDonnell, Senior Director, Technical Affairs, Jay's Close, Viables, Basingstoke, Hampshire RG21 3DP, UK.
Tel: +44 (0)1256 866560; Fax: +44 (0)1256 866502
email: gerry_mcdonnell@steris.com

Good transportation practice

Detlef Werner
Manager QM / R&D, Hanns G Werner GmbH & Co. KG, Tornesch, Germany

The manufacture and control of a medicinal product and the preliminary stages are subject to stringent quality requirements. The increasingly important transportation between the parties involved in the supply chain, has, however, been only partially regulated to date. The author outlines the risks of transportation for the quality of the pharmaceutical materials and suggests that any problems can be resolved through the implementation of Good Transportation Practice. This is an interdisciplinary concept that accompanies a medicinal product from the development stage to dispensing in order to ensure that the quality of the products in question is maintained during transportation. The options available are discussed but these should always be considered in the light of the risk involved and not as an end in themselves.

Herstellung und Kontrolle eines Arzneimittels und seiner Vorstufen unterliegen strengen Qualitätsanforderungen. Der immer wichtigere Transport zwischen den Beteiligten ist aber bisher nur ansatzweise geregelt. Der Autor stellt die Risiken des Transports für die Qualität pharmazeutischer Materialien dar und schlägt als Lösung die Good Transportation Practice vor. Dies ist ein interdisziplinäres Konzept, das ein Arzneimittel von der Entwicklung bis zum Patienten begleitet, um dessen Qualität auf den Transportwegen zu erhalten. Es werden die möglichen Maßnahmen

erläutert, die aber immer in einer vernünftigen Relation zu dem ermittelten Risiko bleiben sollen und nicht zum Selbstzweck werden dürfen.

Key words: good transportation practice, supply chain, logistics, distribution, damage in transit, water vapour sorption, temperature cycling study, data logger

Corresponding author: Detlef Werner, PhD, Hans G Werner GmbH & Co. KG, Hafenstrasse 9, 25436 Tornesch, Germany. Phone: +49-(0)4122-9576-33;
Fax: +49-(0)4122-55205; email: Dr.Werner@pharm-a-spheres.com

Sampling and preparation techniques key to success in meeting new requirement for particulate analysis in SVPs

Joe Gecsey and Tony Harrison
Life Science Application Manager and Pharmaceutical Market Manager, Hach Ultra Analytics, Chesterfield, UK

Effective 1 April 2005, Version 5.1 of the European Pharmacopoeia requires that dosage forms of parenterals less than 100ml be inspected for liquidborne particles using an optical particle counter or, in certain case, an optical microscope. Previously the EP required particulate analysis only for dosage forms greater than 100ml. The test procedure for Small Volume Parenterals (SVPs) in containers under 25ml has been in place within the EP for a number of years [Section 2.9.19, Test 1.B] but until Edition 5.1 testing was not required for dosage forms equal to or less than 100ml. This revision brings testing of European parenteral products more closely into harmony with the existing American USP, Japanese JP and Korean KP regulations.

Key words: Particulate analysis, small volume parenterals, optical particle count

Corresponding author: Tony Harrison, Hach Ultra Analytics, Unit 4 Holmewood Business Park, Chesterfield Road, Holmewood S42 5US, UK
tel: +44 (0)1246 599760; email: tony.harrison@hachultra.com

A safe pair of hands – How secure are your cleanroom gloves used for aseptically prepared pharmaceutical products ?

T Eaton
Sterile Manufacturing Specialist, AstraZeneca, Macclesfield, UK

A punctured glove presents a potential route of microbial contamination during the aseptic preparation of pharmaceutical products. The commonly adopted measure to control this risk is for operating personnel to wear two pairs of gloves, although there is little available information to directly support the effectiveness of this method. A programme of work has been conducted to determine the holing rates of both inner and outer gloves that had been removed from cleanroom personnel after aseptic manufacturing activities. When compared with the holing rate obtained for unused gloves, both the inner and outer gloves were shown to have an increased level of puncture. However, the punctures to the outer glove were found to have not penetrated the corresponding inner glove and a physical barrier of the hand had been preserved. Double gloving has therefore been confirmed to be an effective control method to minimise the risk of product contamination resulting from ruptured gloves.

Key words: aseptic manufacture, latex gloves, glove holing

Corresponding author: Tim Eaton, Sterile Manufacturing Specialist, AstraZeneca, UK Operations, Silk Road Business Park, Macclesfield, Cheshire. SK10 2NA, UK Email: tim.eaton@astrazeneca.com
Telephone: +44(0) 1625 514916; Fax: +44(0) 1625 517750

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Consecutive replicate contact plate sampling assists investigative characterisation of surface-borne bioburden

Edward C Tidswell, Melissa Bellinger, Doug McCullough, Amanda Alexander
Eli Lilly and Co., Indianapolis, IN, USA

Contact plate sampling is a proven and established activity assisting in the management of the controlled cleanroom environment. The technique may, however, be inadequate for the investigative sampling of unusual, potentially soiled surfaces. Consecutive replicate contact plate sampling was used to sample soiled, contaminated taped surfaces of mobile pharmaceutical manufacturing vessel castors. Recovered colonies were enumerated, and the most prevalent isolates speciated. Single contact plates failed to recover

all viable micro-organisms; two species of micro-organism were only recovered onto a second replicate contact plate. Under specific circumstances consecutive replicate contact plate sampling may represent a more appropriate means of evaluating surface-borne bioburden for investigative and risk assessment purposes.

Key words: Consecutive contact plates, bioburden, recovery, risk assessment

Corresponding author: Dr Edward C. Tidswell, Sterility Assurance Leader, Eli Lilly & Co., 1400 West Reymond St., Indianapolis 46221 USA. Telephone: +1 (317) 277-9818; Email: tidswell_edward@lilly.com

Detection of micro-organisms in compressed gases and the validation of a new pressure gas sampler: MAS-100 CG®

R. Ewald1, R. Meier2 and H. Zingre3
1 Swiss-Royal-Consulting, Binningen, Switzerland
2 Independent Microbiology Consultant, Reitnau, Switzerland
3 CEO, MBV AG, Staefa, Switzerland

In a specially developed nebulising chamber, a spore-containing aerosol was generated under pressure. The bacterial spore count of the aerosol was determined by the membrane filtration method and by means of an air sampler for pressure gases (MAS-100 CG®). Based on three different test series, it could be proven that both test methods yielded statistically significant, reproducible results.

(Presented at the 5th European Parenteral Conference of ESPC in Linköping, Sweden.)

Key words: Compressed gas, validation, micro-organisms in gas

Corresponding author: Hans Zingre, MBV AG, CH-8712 Staefa, Switzerland Tel.: +41 44 928 30 80; email: h.zingre@mbv.ch

The quality systems approach to real compliance – a US point of view

Russell E Madsen
President, The Williamsburg Group, LLC, Gaithersburg, Maryland, USA

In the pharmaceutical industry we think of compliance as following procedures, validating and documenting critical processes and operations, conforming with the CGMP regulations, and avoiding regulatory citations. Compliance based on this model is regulatory compliance. However, there is a fundamental difference between regulatory compliance and product quality. Product quality can be broadly defined as “fitness for use” or “fitness for intended purpose.” Regulatory compliance is simply compliance with regulations and guidelines. Compliance with regulations may or may not result in a quality product; it is certainly possible to have one without the other. When the two concepts are aligned, however, manufacturing efficiency is optimized, the consumer receives the highest quality product at the lowest cost, and real compliance is achieved.
Please note the wording “Regulation” in this article refers to FDA CGMP regulations
The wording Regulation(s) in EU terms means legal acts, which are directly applicable and do not have to be transposed into national law but confer rights or impose duties on the Community citizen in the same way as national law1.

Key words: quality, compliance, GMP, PAT

Corresponding author: Russell E Madsen, President,
The Williamsburg Group, LLC, 18907 Lindenhouse Road, Gaithersburg, MD 20879, USA. Phone/Fax: +1 (301) 869-5016;
email: madsen@thewilliamsburggroup.com;
www.thewilliamsburggroup.com

Influence of liquid nitrogen on filter integrity

Leesa D McBurnie, Barry Bardo and Herbert Reichert*
Meissner Filtration Products, Inc., Camarillo, California, USA
* *Meissner Filtration Products, Inc., Nierstein, Germany*

Liquid nitrogen (LN2) is employed in the pharmaceutical industry in lyophilisation baths and for quick-freezing of pharmaceutical preparations. While generally presumed sterile because of its extremely low temperature, LN2 has been associated with an outbreak of hepatitis B, and incidences of Aspergillus and Bacillus contamination. Sterile filtration of LN2 and its validation are problematic because of the >300°C temperature range to which the polymeric filters are exposed. This article reports on LN2 sterile filtration and special operating procedures for successful sterile filtration of LN2.

A three-phase process validation methodology is described. Results serve to validate the efficacy of the sterile filtration of LN2 under conditions described in this article. Validation of the sterile filtration of LN2 process is readily achievable by pharmaceutical and biopharmaceutical companies using the methods we describe.

Key words: Sterile filtration, liquid nitrogen filtration, LN2, filter validation, Brevundimonas diminuta

Corresponding author: Barry Bardo, Meissner Filtration Products, Inc. Camarillo, California 93012, USA. email: Barry.Bardo@Meissner.com