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Erratum: The paper "Think global… but act local" in the last issue of the journal (2003, Vol 8 No 4, page 95) carried the wrong abstract. It should have been the first two paragraphs of the article as printed.

Instructions for authors in Vol 8 No 2

Application of dry-scrubbing air filtration to control airborne molecular contaminants in the pharmaceutical, biotechnology and life science industries

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Air handling systems serving biotechnology, pharmaceutical, and life science cleanrooms are designed to provide and maintain environments sufficiently well-controlled as to minimise process defects, assure product quality, and to provide for worker safety and health. They also must control what contaminants are emitted from their facilities to be environmentally

conscious organizations as well as comply with local regulations. This allows them to maximize yields and success rates and avoid interference from regulatory agencies. The large majority of such systems are designed to provide contaminant-free manufacturing environments by maximising the control of airborne particulates - both viable and non-viable. However, there is another important type of airborne contaminant that is not controlled with traditional filtration technology. This is the non-particulate, or molecular, contaminant.

Outdoor air quality has become much more important for advanced biotechnology processing (e.g., DNA-chips, gene chips). Ozone levels as low as 5-10 parts per billion (ppb) have been reported to cause yield problems.1 Air quality has also become more important to personnel and government agencies. Therefore, pharmaceutical processes have employed dry-scrubbing systems to deal with contaminants that cause odor problems, health problems, or are detrimental to the environment.

This article will describe the application of dry-scrubbing media in these arenas. However, a brief introduction of airborne molecular contaminants (AMC) will be given first to familiarise the reader with the types of contaminants that are being discussed.

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Microbiological contamination models for use in risk assessment during pharmaceutical production

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This paper describes the fundamental mechanisms of microbial contamination during manufacture of pharmaceutical products. Models are derived that describe air and surface contact contamination. These models can be used to develop and improve methods of microbial risk assessment. The use of the FMEA (FMECA) method of risk assessment is discussed and, when used with the correct risk factors, its use endorsed.

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Microbial risk assessment in pharmaceutical cleanrooms

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The microbial risk to aseptically manufactured products in pharmaceutical cleanrooms can be assessed by the use of fundamental equations that model the dispersion, transfer and deposition of microbial contamination, and the use of numerical values or risk descriptors. This can be done in two-stages, with the first stage used to assess the transfer of contamination from all of the sources within the cleanroom suite and the second stage used to assess both air and surface contact contamination within critical production areas. These two methods can be used to assess and reduce microbial risk at the preliminary design stage of the cleanroom and associated manufacturing process or, retrospectively, for an established manufacturing operation.

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Hygienic risks caused by microorganisms trapped between closure and vial neck

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In certain circumstances microorganisms trapped between the vial neck and closure are able to withstand the saturated steam atmosphere of a sterilization cycle. Under growth-promoting conditions, residual organisms may result in contamination of the product. In the manufacture of sterile products, appropriate hygiene of the primary packaging material must be guaranteed by sterilization. Normally, sterilization is performed using the pharmacopoeial reference cycle of 121°C for 15 minutes. This cycle is not always sufficient to demonstrate a sterility assurance level (SAL) of 10-6 with bioindicators because of increase in the thermoresistance of bacterial spores, expressed as the D121 value, which is markedly increased compared to the control group, particularly in contact with closures.

Mikroorganismen, die zwischen Falschenhals und Verschlussstopfen eingeschlossen werden, sind unter Umständen der Sattdampfatmosphäre eines Sterilisationszyklus nicht zugänglich. Unter Wachstum begünstigen Bedingungen können verbleibende Keime zur Kontamination des Produktes führen. Bei der Herstellung von sterilen Präparaten ist durch eine

Sterilisation eine geeignete Hygiene der Primärpackmittel sicherzustellen. Üblicherweise erfolgt die Sterilisation unter Anwendung des pharmakopöalen Referenzzyklus bei 121°C über 15 Minuten. Dieser Zyklus reicht nicht in allen Fällen aus, um eine Sterilisationssicherheit (SAL) von 10-6 mit Bioindikatoren zu belegen. Grund dafür ist ein Anstieg der Thermoresistenz von Sporen, ausgedrückt als D121-Wert, der insbesondere im Kontakt mit Verschlussstopfen deutlich gegenüber der Kontrollgruppe ansteigt.

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Contents and Abstracts

Validation – How valid?

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This paper is an attempt to take an objective look at the topic of Process Validation, to examine where we are now, how we got here and where we are going, and to try to extract from this much-abused and distorted concept what is truly rational and valuable about it.

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Risk profiling pharmaceutical manufacturing processes

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Risk assessments are establishing fundamental roles in the quality assurance of all pharmaceutical manufacturing processes; moreover they are gaining recognition as possible mechanisms aiding regulatory inspection. All risk assessments demand a numerical quantification of risk, however derivation of the values are often prone to a degree of subjectivity leading to inexactitude. Risk assessments augmented with risk profiling represent a means of somewhat removing the emphasis placed on numerical values originally derived empirically. Risk profiling represents a means of improving patient safety, process design, the rationalization of validation activities and may well be integral to the next phase of cGMPs.

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Right, not just first time, but every time

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Any facility that is being designed and built today must be assumed to have a useful life of 10 – 15 years. Hence it is critical to design the facility in such a way that it will be fit for purpose throughout that time period. A review of parenteral manufacturing over the past fifteen years reminds us how rapidly things can change in this highly technical industry. Some of the predictions for how the pharmaceutical market is going to change in the next fifteen years have significant implications for manufacturing. Traditional attitudes can also create barriers to flexibility and need to be broken down. One of the most powerful tools in ensuring that the design of the facility is appropriate is the User Requirement Specification. Reviewing the questions that are asked in a typical URS and answering them fully will facilitate an effective design process and make it more likely that the facility will still be effective fifteen years from now.

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Contents and Abstracts

Assessing microbial risk to patients from aseptically manufactured pharmaceuticals

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The microbial risk to patients from aseptically manufactured pharmaceuticals is dependent on the chance that a product contains sufficient microbes to initiate an infection. This possibility is dependent on risk factors associated with the method of production and product formulation, and can be

calculated. An analysis of these risk factors can be used to minimise patient risk and assist in determining the appropriate level of contamination control required for manufacturing.

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Short Communication

Gas/vent filters – practical factors to consider

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Gas/vent filters are a necessary part of the equipment required to undertake sterile manufacturing. This paper considers factors to be taken into account in the selection, validation and routine use of such filters and makes recommendations addressed to users.

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Cleanroom dressed people as a contamination source: some calculations

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Results are reported from tests carried out with clothing systems which have passed through 1, 25, and 50 washing/sterilizing cycles, respectively. With these results, some calculations are given, describing predicted contamination levels in cleanrooms with turbulent mixing air and cleanrooms with vertical unidirectional air flow when people are dressed in modern cleanroom clothing systems washed several times.

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case study

Process simulation/media fill

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This is a report of a meeting organised by Novartis Pharma, Aargau, Switzerland for the German-speaking pharma industry on the subject of process simulation/media fills. The aim was to establish a consolidated basis regarding performance, reconciliation and requirements of process simulations (media fills).

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Understanding past and proposed changes to the USP Chapter <643> total organic carbon

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Contents and Abstracts

Important aspects of regulatory requirements on primary packaging materials for pharmaceutical use in EU

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The article reviews important requirements on primary packaging materials for pharmaceutical use. Regulatory requirements from EU Directives, the European Pharmacopoeia (Ph. Eur.) and Notes for Guidance are listed. Moreover the connection to foodstuff regulations and international standards is explained. The background of the requirements is illustrated in the general sections, which refer especially to several kinds of interaction between the pharmaceutical preparation and its immediate packaging. Aspects concerning the different kind of dosage forms are discussed. Several materials not stated in Ph.Eur. are listed and are proposed for the elaboration of new chapters.

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The auditing of glass tubing manufacturers

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Glass containers are still extremely important for the production of parenteral products. Glass tubing is practically the sole raw material for the manufacture of primary packaging materials made of tubular glass. Consequently, the qualification of glass tube manufacturers is the absolute main focus of supplier audits. The manufacturer of primary packaging materials made of tubular glass can only be successful if the high quality of his raw material can be consistently ensured.
This paper addresses auditing glass tube manufacturers on a European level. The aim of the audits is the incorporation of GMP-relevant requirements into the production and control of primary packaging materials for medicinal use.

Glascontainer haben für die Herstellung von Parenteralia nach wie vor einen außerordentlich hohen Stellenwert. Röhrenglas ist praktisch einziges Ausgangsmaterial bei der Herstellung von Packmitteln aus Röhrenglas. Die Qualifizierung der Glasröhren-Hersteller ist somit der Schwerpunkt der Lieferanten-Auditierung schlechthin. Der Hersteller von Primärpackmitteln aus Röhrenglas kann nur erfolgreich sein, wenn konsistent die hohe Qualität seines Ausgangsmaterials gesichert ist.

Im vorliegenden Beitrag wird auf das Auditieren von Glasröhrenherstellern auf europäischer Ebene eingegangen. Ziel ist die Berücksichtigung von GMP-relevanten Anforderungen bei Produktion und Kontrolle von Primärpackmitteln für Arzneimittel.

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The assessment of closure efficiency

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The total 'effectiveness' of most packs, certainly from a functional performance point of view, is frequently related to the closure system employed. In the case of impermeable materials, e.g. metal and glass, pack efficiency is largely dependent on the closure. With permeable materials such as plastics, egress and ingress may occur both via the pack itself and the closure system employed. However, total pack efficiency must consider factors other than ingress and egress, hence these need identifying before the assessment of closure efficiency can be fully discussed. As the importance of each factor will vary according to the product and the pack involved, the order given below has not any particular significance.

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Pharmaceutical primary packaging materials made of tubular glass from the aspect of drug safety and product applications

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Safety is the top requirement in the selection of primary packaging materials for pharmaceutical products. The aim of this paper is to provide a review of the manufacturing options for these glass packaging materials, particularly with respect to future applications. Tubular glass provides a sound basis for small-volume packaging units for this purpose.

The stringent requirements placed on these containers include not only accuracy of diameter and wall thickness, but also high resistance to the product properties and the ability to inspect the contents readily – even

where brown glass is selected for light-sensitive products. Complex processes and equipment are already used in the initial step, i.e. the production of the tubular glass. This assures the quality of the final containers, manufactured by subsequent forming processes.

The underlying assumption for these processes is that the current requirements for these forms of packaging are likely to undergo changes and updates in the future, as evidenced by the switch over from ampoules and injection vials to pen systems and the cartridges used for them, as well as prefillable disposable syringes for injectables.

The DIN and ISO standards have been very helpful in this context. Individual prefillable syringe systems for special requirements and routes of administration have also been developed. The fact that a high quality standard is achieved in this way should be self-evident; further support is provided by extended regulations such as the ISO 9000 series, which includes quality management, and the planned ISO Standard 15378 which provides a link with Good Manufacturing Practice (GMP) in the production of these primary packaging materials.

Sicherheit ist oberstes Gebot bei der Auswahl von Primärpackmitteln für pharmazeutische Produkte. Diese Veröffentlichung soll einen Überblick über die Möglichkeiten der Herstellung solcher Glas-Verpackungen geben, insbesondere im Hinblick auf zukünftige Applikationsarten. Das Röhrenglas ist deshalb eine solide Basis für die Auswahl kleinvolumiger Verpackungen für diese Zwecke.

Nicht nur die Genauigkeit im Durchmesser und der Wanddicke, auch die hohe Resistenz und Prüfbarkeit des Inhaltes - selbst bei der Wahl von Braunglas für lichtempfindliche Präparat – entsprechen den hohen Anforderungen an solche Behältnisse. Bereits bei der Produktion des Röhrenglases werden aufwendige Verfahren und Einrichtungen eingesetzt, um die Qualität der in einem weiteren Verformungsprozess endgültig hergestellten Behältnissen zu gewährleisten.

Dabei wird davon ausgegangen, dass aufgrund der schon jetzt bestehenden Anforderungen an solche Verpackungen ein gewisser Wandel von den bisher üblichen Standards wie Ampullen und Injektionsflaschen zu Pen-Systemen und den dabei eingesetzten Zylinderampullen (Cartridges) sowie vorgefüllten Einmalspritzen (prefillable disposable syringes) für Injektionspräparate zu erwarten ist.

Dabei ist die Standardisierung im Rahmen von DIN – und ISO-Normen eine erfolgreiche Hilfe. Zusätzlich ergaben sich im Laufe der Zeit Entwicklungen von einzelnen Spritzensystemen für besondere Anforderungen und Applikationsarten.

Das dabei ein hoher Qualitätsstandard erreicht wird dürfte selbstverständlich sein und wird durch erweiterte Vorschriften wie z.B. der ISO 9000-Reihe mit Qualitätsmanagement und dem geplanten ISO Standard 15378 als Verbindung zu Good Manufacturing Practice (GMP) bei der Herstellung solcher Primärpackmittel unterstützt.

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The purchase of pharmaceutical packaging materials and rationalisation of inspection procedure

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The manufacturers of pharmaceuticals bear overall responsibility for their product. This means that, consequently, they also assume liability for labelling and packing materials which, although not produced by them, are an essential part of a medical preparation. In view of the impact that pharmaceuticals can have on the life and health of a patient, it is imperative that the product in its entirety is subject to monitoring. The present article deals with the legal bounds in the question of delegating compulsory inspection procedure as far as possible to the supplier.

The article is based on the German legal situation, but it is also relevant for other European countries as the provisions within the European Union have been harmonised to a great extent. The issue of product liability under civil law is a case in point, having been standardised in the “Directive of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products” (Official Journal, L 210, dated 7 August 1985, page 29 et seq). The specific aspects relevant to the law governing medical preparations are given in the EU-GMP Guideline and the supplementary guidelines for sampling of source materials and packing materials.

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EU GMP Annex 1 – ISO 14644-1 – FDA Aseptic Guidance Is this a good basis for an International Sterile Products GMP?

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This paper explores the relationship between current good manufacturing practices (cGMPs) for sterile products and the new ISO cleanroom standards, identifying an amalgam that will satisfy all regulators.

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