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Harmonisation of conductivity tests for Pharmaceutical Waters

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The chemistry tests to verify the quality of bulk Pharmaceutical Waters underwent substantial changes with the implementation of USP 23 in 1996. These qualitative tests were replaced with modern, quantitative, instrument-based tests such as conductivity and total organic carbon (TOC). The acceptance of these changes was not without its problems, but the resulting changes have improved Pharmaceutical Water quality control. Subsequently, the European Pharmacopoeia (EP) implemented its versions of conductivity and TOC tests for Pharmaceutical Waters.
The conversion to these instrument-based tests represented a significant step towards unifying the tests for these EP and USP waters. The USP TOC monograph (<643>) is substantially identical to its operation and implementation in the EP (2.2.44). Interestingly, the less complicated and more technologically robust method of conductivity greatly differs between the USP and EP. The reasons for these differences are based on different application strategies. The similarities in these strategies are discussed. However, the practices espoused in the EP standard possess some technical faults or uncertainties which require reconsideration based on the science behind the water chemistry and conductivity.

Part of this paper was presented at The Parenteral Society meeting on September 14, 1999 in London, UK.

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Pharmaceutical isolator leak testing – proposal for specification of leak test rates which allows a comparison of quoted values

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At present, most isolator manufacturers quote leak rates in pressure drop/rise per unit time. This does not, however, allow a true comparison, as the tests are frequently performed at different test pressures, i.e. 1000 Pa above or below atmosphere compared with 250 Pa above or below atmosphere. Furthermore, it gives no idea of leak rate volume per unit time. This is important, as it is difficult to picture a Pascal of pressure leaking, whereas an operator can picture a volume (i.e. the number of cc's), allowing him or her to make a judgement on the contamination that could be going in or out of the containment. The proposal in this paper is to provide a

standardised leak rate in terms of an agreed standard pressure (not necessarily the test pressure) and volume leaked in cc per unit of time (i.e. leak rate = kPa cc/sec).

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Freeze-drying – a review

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This paper is a general review of the freeze-drying process and the freeze-dryer, primarily in the pharmaceutical arena. After defining freeze-drying, the rationale for the use of this process is discussed. The salient points of the three phases of freeze-drying are identified. The evolution of the freeze-dryer is described and the GMP implications of this evolution are noted and described. Present and future developments, notably loading systems, are discussed and the two goals of freeze-dryer development are identified. However, it is noted that these two goals are unlikely to find favour in the pharmaceutical marketplace.

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Scanning electron and atomic force microscopy for the sizing of bacterial populations

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Microporous membrane filtration is routinely used in the laboratory and in pharmaceutical manufacturing plants for the sterilisation of aseptic processed drug products and other solutions. Currently, Brevundimonas diminuta is used as a standard challenge organism to validate 0.2/0.22-mm rated "sterilising grade" filters and most commonly applied in "worst case" (parametric) drug product specific challenges to validate filtration sterilisation processes. However, other organisms that may be more penetrating and

presumptively smaller than B. diminuta are often identified as bioburden and therefore sizing of bacteria becomes an important criterion for appropriate membrane filter selection. Most commonly, bacterial populations are sized by scanning electron microscopy (SEM). The average size of a cell in a population of B. diminuta ranges from 0.32-0.35 by 0.82-0.96 mm1 when measured by SEM. The potential effect of preparation methods on size measurements is unresolved. We have also been investigating the use of atomic force microscopy (AFM), a technique that does not require extensive sample manipulation and dehydration, for sizing. Using AFM, our initial observations for the average B. diminuta cell size is 0.609 ± 0.084 mm by 1.077 ± 0.185 mm. These data suggest that dehydration during sample preparation for SEM may lead to smaller apparent size. Previous work has demonstrated that Ralstonia pickettii, a common bioburden organism, can penetrate 0.2- and 0.22-mm rated filters if exposed to certain pharmaceutical process conditions2. SEM and AFM sizing data for populations of R. pickettii are presented and the relative merits of both techniques are discussed.

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Short communication

The use of modular concepts in the construction of a parenteral pharmaceutical facility

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The recent development of a modular approach for delivering a complete pharmaceutical manufacturing facility has resulted in technical and business advantages over conventional construction. A case study of a liquid parenteral formulation and fill facility for Eli Lilly, Egypt is presented here.

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Harmonising the training of Qualified Persons in Europe

A review of the role and status of the Qualified Person (QP) throughout Europe

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In this paper, the author considers the different ways in which Qualified Persons (QPs) are trained and appointed in various Member States of the EU. He examines some of the basic differences between The Pharmacien Responsable in France as compared to the QP in the UK. The outline syllabi of pharmacy degrees are discussed in the light of EC Directive educational intentions. The author presents a short review of how a number of Member States train and appoint their QPs. Finally, he suggests possible routes for overcoming the procedural differences between Member States in order to rationalise training and appointment of QPs throughout Europe.

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Pressure differential testing of sealed vials containing freeze-dried product

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An in-house requirement to carry out 100% inspection of vials of freeze-dried product for leaks resulted in the search for a suitable method that could be validated and that was capable of a high throughput rate. This paper presents findings from the method selection process, and a description of the methods and results of a successful validation exercise on the selected automated Wilcomat R18F Pressure Differential Tester, using a proceduralised dye bath test method as a reference point. A brief explanation of the machine operating principles and summary of operating experience are also presented.

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Risk assessment in the manufacture of medicinal products based on Design and Barrier Assessment (DaBA)

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Risk assessment in context of GMP and validation has been discussed for a number of years but not applied to the manufacture of medicinal products in reality. The reason for this may be that established methods are general, rather than being configured to focus on aspects that may adversely affect product quality. In spite of this, there is no doubt that risk assessment will be an important decision tool with regard to criticality; one suitable method could be Design and Barrier Assessment, based on the principles of HACCP and configured to focus on product safety and efficacy.

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Opinion Paper

The future of aseptic processing of healthcare products

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There are two processes by which pharmaceutical products labelled sterile are manufactured, aseptic processing and terminal sterilisation. In current regulatory guidance and industry standards, the terms "aseptic" is often used interchangeably with the term "sterile", although scientifically, the words have very different meanings, aseptic being free from pathogens, rather than sterile. Aseptically manufactured products require the exclusion of micro-organisms from the product stream and from the environment in which the product is filled or assembled.
Given the necessity of human operator involvement in aseptic manufacturing in conventional cleanrooms, aseptically produced products have been considered less safe than terminally sterilised products. However, the emergence of new advanced manufacturing technologies that effectively eliminate the likelihood of human-borne contamination in product filling or assembly may usher in an era in which the safety of products manufactured using exclusion technologies is so close to that of sterilised products, that the difference can be considered negligible from a consumer safety perspective. The continued evolution of clean manufacturing environments will have profound effects on product manufacturing regulation and testing requirements within the next decade. This article examines the potential of the new technology and the changes its implementation promises to bring to sterile product manufacturing.

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Short Communication

Towards a 'human pyrogen test'

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In the twenty years or so since an in vitro pyrogen test based upon the human fever reaction, a 'human (in vitro) pyrogen test', was first considered, a number of variants of this test have been developed and are at various stages of development. These are reviewed below.

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Short Communication

Integral calculus to evaluate decontamination times in isolators

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The first rules for calculating decontamination of isolators based on research conducted over a number of years are described. The work sheds some light on the results obtained using LOGI-STER-2SR for decontamination of isolators by means of chemical vapour.
Some data are omitted for commercial confidentiality reasons.

Les travaux entrepris par GMI depuis plusieurs années permettent aujourd'hui d'énoncer les premières lois de calcul concernant la décontamination des isolateurs. Certes, pour des raisons de concurrence, tout ne sera pas dit.
G.M.I. donne ici quelques éléments sur ses résultats obtenus avec LOGI-STE-2SR pour la décontamination des isolateurs par vapeur chimique.

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High hydrostatic pressure (HHP): An alternative method of sterilisation and decontamination of fragile drugs?

Y. Rigaldie1,2,3, G. Lemagnen1, A. Largeteau2, D. Larrouture1, M. Abba1,3, C. Durandeau1,
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The aim of this study was to investigate the use of HHP technology as a possible alternative method for the decontamination and sterilisation of fragile drugs. We demonstrated the safety of HHP treatment on several fragile biomolecules (molecular weight from 1200 to 150 000 g/mol: two peptides, insulin and antibodies). A HHP treatment (10 min at 400 MPa) inactivates pure suspensions of Pseudomonas aeruginosa and Candida albicans. HHP at low temperature induces a stronger inactivation than at room temperature. Staphylococcus aureus needs a longer duration of HHP treatment to be totally inactivated. Since the vegetative cells of endospores appear to be barosensitive, further research is being carried out on inducing the germination of Bacillus subtilis spores under HHP.

L'objet de ces travaux est d'étudier l'utilisation de la technologie des Hautes Pressions comme une méthode alternative potentielle de décontamination et de stérilisation des molécules fragiles. Nous montrons l'innocuité du traitement HP sur différentes biomolécules fragiles (poids moléculaire croissant de 1200 à 150 000 g/mol : deux peptides, de l'insuline et des anticorps). Un traitement sous hautes pressions (10 min à 400 MPa) permet d'inactiver totalement des suspensions pures de Pseudomonas aeruginosa et de Candida albicans. Le traitement HP appliqué à basses températures induit une plus forte inactivation qu'à température ambiante. Staphylococcus aureus nécessite un temps de traitement plus long pour être inactivé. Comme les formes végétatives des endospores semblent être barosensibles, plusieurs protocoles de germination par HP des spores de Bacillus subtilis sont actuellement à l'étude.

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Air treatment systems in the pharmaceutical industry

Part I: General aspects of design, filtering and air conditioning

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Nowadays, air and water are deemed to be fundamental to the quality of manufactured pharmaceutical products. Thus, air and water treatment systems must be integrated into the relevant industrial manufacturing process and fully validated. These papers (Parts I and II) attempt to bring up to date the air treatment process in a pharmaceutical industrial plant manufacturing non-sterile medicinal products. Part I considers general aspects of design, filtering and air conditioning. In Part II, various examples of clean-room air conditioning are presented.

Hoy día el aire y el agua en la Industria Farmacéutica, se consideran básicos para la calidad de los productos que se fabrican. Por ello los sistemas de tratamiento de aire y agua han de estar integrados en el proceso de fabricación industrial de medicamentos y han de estar validados. El presente trabajo, pretende ser una puesta al día, del tratamiento de aire en una Planta Industrial Farmacéutica de fabricación de medicamentos no estériles. En una primera parte (parte I), se trata de consideraciones generales, de diseño, filtración y climatización. En una segunda parte (parte II) se muestran ejemplos de climatización de salas limpias.

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The bacterial endotoxins test: past, present and future

Dr James F Cooper
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The bacterial endotoxins test (BET) became the test of choice for detecting pyrogen in parenterals because of its simplicity, sensitivity and specificity. A harmonised BET that simplified and included all LAL methods became effective in 2001. Future revision may include certification of endotoxin standards, tighter acceptance criteria for kinetic LAL methods and sample preparation by concentration. Endotoxin alert limits are proposed for starting

materials to reduce the risk of pyrogenic products. Broad use of the BET in process control has enhanced the microbiological purity of finished products.

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Modulated temperature differential scanning calorimetry and its application to freeze-drying

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MTDSC is a software modification of the traditional DSC thermal analysis technique that allows more accurate determination of the glass transition as well as measurement of the endothermic relaxation that often accompanies the transition. The glass transition is an essential parameter both of the original frozen solution and of the end product. Measurement of endothermic relaxation allows the determination of molecular relaxation times in the freeze-dried product that may be useful in predicting the effect of formulation variables and storage conditions on physical stability.

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Annex 17 – Parametric release:

A review from the perspective of a

Qualified Person

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This paper evaluates Annex 17 'Parametric Release', published in the EU, which provides the first guidance within Europe as to how manufacturers can reduce finished product testing. It critically examines the removal of sterility testing, and the removal/reduction of finished product testing and raw materials testing. Although such removals or reductions are of great interest to many manufacturers, the steps required to effect such a process and to

achieve regulatory approval are considerable. The paper looks at each situation and examines the requirements and, in particular, their impact on the Qualified Person, who, at the end of the day, is responsible for releasing product produced under such a regime.

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Contents and Abstract

Introduction to this special issue

Microbiological aspects of parenteral production: recent developments

Norman Hodges and Geoff Hanlon, guest editors
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Microbiological environmental monitoring in today's industry

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Increasing emphasis has been placed on environmental monitoring over recent years when, at the same time, there have been improvements in general facility design, use of isolator technology and greater focus on operator training. In recognising the limitations of the monitoring techniques available to the microbiologist, which have not changed over time, it is important that the monitoring programme is appropriately targeted and the use of HACCP, as a process management tool, is increasingly topical.

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Product testing

Rosamund Baird
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The purpose, interdependence and limitations of bioburden testing, sterility testing and parametric release in the manufacture of sterile pharmaceutical products are considered in this article. Test methods are also discussed.

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Viable but non culturable (VBNC) microorganisms in the pharmaceutical industry – their significance and detection

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The purpose of this paper is to assess the potential significance of Viable but Non Culturable (VBNC) micro-organisms in the pharmaceutical industry. Consideration is given to the nature of the VBNC state. Current methods for the detection of such organisms are outlined and potentially significant new methods, which may impact the industry, are considered. The significance of VBNC organisms on the future direction of pharmaceutical microbiology is discussed.

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Biological Indicators: friends or foes?

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There is a growing concern in the pharmaceutical and healthcare industries over the selection, use and properties of Biological Indicators (BIs) for the validation and monitoring of sterilisation processes. BIs possess a known sterilisation resistance and are used to assess the microbial lethality of a given sterilisation process. Collectively, they are well-characterised populations of bacterial endospores, their selection being governed principally by their high resistance to specific sterilisation processes in relation to the indigenous microbial bioburden. Specific strains are used for the validation of steam, dry heat, radiation and ethylene oxide and monitoring of ethylene oxide sterilisation processes. In theory, therefore, BIs provide a well-defined, reliable but crude method of assessing process effectiveness microbiologically. However, there is a counter-balance to these positive attributes, brought about by variability in sterilisation process development and validation, and variability in the resistance properties (D-values) of the BIs. A change in D-value occurring between process validation and re-validation may result in different probabilities of BIs surviving on the second or subsequent validations or revalidations. Possible reasons behind such BI variability are discussed and potential ways forward proposed.

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Sterilisation of biotechnology products

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Biotechnology products are a heterogeneous group of pharmaceuticals derived from prokaryotic or eukaryotic cell culture and are typically heat-labile peptides, proteins or nucleic acids. As such, they are not amenable to terminal sterilisation by heat or other processes which damage biopolymers. Biotechnology products are, therefore, almost without exception, sterilised by submicron filtration and filled and finished using aseptic processing.
The physical and chemical attributes of biotechnology products present a special challenge to the filtration process, demanding stringent control if product safety is to be assured.
The potential applicability of other means of sterilisation, such as nanofiltration and high-intensity, broad-spectrum pulsed light is critically discussed. Whilst these techniques may one day improve the assurance of sterility of this important group of products, their current utility is, at best, limited.

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Coping with leaks in pharmaceutical isolators
Pharmaceutical isolators: protection for the product, the operator or both

Brian Midcalf
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Using an isolator may give assurance that a hazardous material, which is to be manipulated, will be separated completely from its manipulator. Further consideration of the isolator solution leads to a number of questions or options that need further consideration. Although this paper concentrates on the issues of handling potent or hazardous materials, isolators are used in many different environments or for different procedures.
An isolator may have a number of different transfer devices and can be constructed with a range of different features, so it is important that the optimum configuration is wisely selected. If we accept the principle that, in

practice, an isolator will leak, and that the substances to be handled are toxic or hazardous, it is likely to be a source of anxiety for the operator. This problem has been raised with the Medicines Control Agency (MCA) and the Health and Safety Executive (HSE) and a preliminary study has been completed. This study looked at the contamination levels of a cytotoxic agent in the workers using either a positive or negative pressure isolator. A survey of the use of isolators has been carried out through the National Quality Control Committee. It is important to keep the perception of leaks in perspective: the safe consideration of the product and the operator may be dependent on this. It is possible to estimate a leak quantitatively and these values could aid the safe use of an isolator.

The text for this paper is based on part of a presentation made at the Parenteral Society Conferenc,e October 2000.

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