



PMF NEWSLETTER

A PUBLICATION OF THE PHARMACEUTICAL MICROBIOLOGY FORUM
Distributed Internationally to 9,440 Subscribers in over 100 Countries

PURPOSE: To provide a forum for discussion of microbiology issues in the pharmaceutical and related industry. The information contained in this newsletter includes the professional opinions of individuals and does not represent the policies or operations of any corporation or government agency to which they may be associated. *PMF Newsletter* is intended to serve as an open forum. The information in *PMF Newsletter* is solely for informational purposes and is developed from sources believed to be reliable. Statements expressed constitute current opinions derived through analysis of available information and professional networking. Articles or opinions are for information only to stimulate discussion and are not necessarily the views of the PMF board or regulatory agencies. The *PMF Newsletter* cannot make any representations as to the accuracy or completeness of the information presented and the publisher cannot be held liable for errors.

Volume 18, Number 1

January, 2012

Letter from the Editor



Welcome to the first issue of the 2012 *PMF Newsletter*!

Letter from the Editor	1
The Use of In-House Microbial Isolates in Compendial Testing	2
Recent Developments in European Regulatory Requirements: Issues Affecting the Microbiologist	5
Upcoming PMF Conferences	10
Upcoming Events	16

In this issue we present a White Paper which provides several regulatory and industry references on the importance of including in-house microbial isolates in compendial testing. For some areas, this has been a long-standing expectation as evidenced by regulatory actions and guidances. For others, we are beginning to see an increasing regulatory expectation.

Dr. Tim Sandle provides a survey of some of the recent developments in European regulatory requirements that have taken place in 2011, including pharmacopoeial changes and inspectorate guidelines. Dr. Sandle has expertly summarized changes that are of interest to pharmaceutical microbiologists.

This issue also carries all 2012 conferences planned by PMF. If you have come to some in the past, you know how good they are and how instructive the discussion and interaction with the speakers and other attendees is when conducted in the small group setting. If you haven't come before, 2012 is your year! Check out the listing on the last page of this newsletter.

We are always interested in your inputs and concerns. Please let us know if there are articles or topics you would like to see addressed in this newsletter.

Bob Westney

rwestney@cryologics.com

Pharmaceutical Microbiology Forum (PMF) 2011 Editorial Board

President/Editor-in-Chief:

Scott Sutton, Ph.D.
Microbiology Network, Inc. USA

Editor

Robert Westney, M.S., RAC, CMQ/OE
Cryologics, Inc.
Westney & Associates Consulting, LLC

Editorial Board:

Ziva Abraham, Microrite, Inc., USA
Phil Geis, Proctor-Gamble, CTFA, USA
Klaus Haberer, Ph.D., Ph. Eur., Germany
Karen McCullough, Roche Labs, LAL User's Group, USA
Paul Priscott, Ph.D., AMS Labs, Australia
Eric Strauss, Teva Pharmaceuticals, Israel

Don't miss!
Open Conference on Compendial Issues - Compendial Guidance in QC Microbiology and CGMP

January 30-31, 2012

<http://bit.ly/yyPYLh>

The Use of In-House Microbial Isolates in Compendial Testing

Robert Westney
Director of Quality and Operations
Cryologics, Inc.

The use of in-house isolates in compendial testing is increasingly becoming a regulatory expectation. This article reviews FDA 483 observations as well as warning letters, regulatory guidance documents, compendial chapters, and industry publications to present the basis for this expectation.

DISINFECTANT EFFICACY

Use of in-house isolates for disinfectant efficacy testing (validation) has been a long-standing regulatory expectation.

FDA 483 Observation

Ben Venue Laboratories, Inc.

May 25, 2011

(<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM275843.pdf>)

“The firm was unable to provide scientific rationale for the use of the selected organisms used in the Disinfectant Efficacy study. These organisms were not representative of organisms isolated from the facility nor were they representative of the USP guidelines.”

FDA Warning Letter

Catalent Pharma Solutions

March 28, 2008

(<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048356.htm>)

"Disinfectant effectiveness studies against representative microorganisms and/or specific in-house isolates were not conducted for cleaning agents used in your facility to disinfect production areas, including aseptic areas."

FDA Memorandum

Review of Biologics License Application
Instituto Bioclon, S.A. de C.V.

(<http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM270551.pdf>)
Regarding Disinfectant Effectiveness Studies: "No rationale was provided for the ATCC organisms used nor was actual EM isolates used for the study."

The FDA provides guidance on the efficacy of disinfectants used in cleanrooms.

Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice

(Continued on page 3)

Accuracy & Traceability
have never been **easier**
or more **affordable**.

ez accu shot™
GROWTH PROMOTION TESTING


Introducing EZ-Accu Shot™, a quantitative microorganism preparation for Growth Promotion Testing.

USP recommended strains • Self-contained kit • Precise CFU count
• Delivers less than 100 CFU per 0.1 mL • 8-hour stability • Easy storage
• No dry ice • Reduced shipping cost • 1 pellet per vial • No forceps required
• Instant dissolve • Little to no prep time • No pre-incubation
• Peel-off Certificate of Assay • On-line Certificate of Analysis • Cost-effective
• Authentic • Traceable

www.microbiologics.com

MicroBioLogics®
Convenience with Confidence

**WHAT DO YOU HAVE TO LOSE BY NOT USING RAPID MICROBIAL METHODS?
JUST TIME AND MONEY.**



New Application
Bioburden screening for vaccine manufacturing

Micro PRO™ DETECTION SYSTEM

Micro PRO™ DETECTION SYSTEM

Specialized Technology for Rapid Microbial Detection

The Micro PRO™ Detection System by Advanced Analytical, the leader in specialized rapid microbial detection, can boost productivity, increase sample throughput, and improve the bottom line.

By delivering

- > fast and accurate results
- > automated high-throughput analysis
- > results that correlate to traditional plate counts
- > 21 CFR part 11 compliant software
- > versatility for a range of applications, including
 - product screening
 - purified water monitoring
 - surface swab analysis
 - pure culture enumeration

Really, what do you have to lose?

To learn more about the versatility of the Micro PRO™ Detection System, please contact us at info-0803@aati-us.com

+1-515-296-6600
Info-0803@aati-us.com
www.aati-us.com/0803



(Continued from page 2)

Food and Drug Administration

September 2004

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf>)

“Routinely used disinfectants should be effective against the normal microbial vegetative flora recovered from the facility... If indicated, microorganisms associated with adverse trends can be investigated as to their sensitivity to the disinfectants employed in the cleanroom in which the organisms were isolated.”

A compendial reference can be found in the United States Pharmacopeia (USP).

USP <1072> Disinfectant and Antiseptics

“... the most frequently isolated microorganisms from an environmental monitoring program may be periodically subjected to use-dilution testing with the agents used in the disinfection program to confirm their susceptibility, as there are real differences among different species in resistance to the lethal effects of different sanitizers.”

“To demonstrate the efficacy of a disinfectant within a pharmaceutical manufacturing environment, it may be deemed necessary to conduct the following tests: (1) use-dilution tests (screening disinfectants for their efficacy at various concentrations and contact times against a wide range of standard test organisms and environmental isolates); (2) surface challenge tests (using standard test microorganisms and microorganisms that are typical environmental isolates, applying disinfectants to surfaces at the selected use concentration with a specified contact time, and determining the log reduction of the challenge microorganisms); and (3) a statistical comparison of the frequency of isolation and numbers of microorganisms isolated prior to and after the implementation of a new disinfectant.”

Several industry publications address the use of in-house isolates in disinfectant efficacy testing.

"Regulatory Aspects Concerning the Quality Controls of Microbiological and Nonviable Particulate Contamination in Pharmaceutical Manufacturing"

Ray T. Oji

Food and Drug Administration

American Pharmaceutical Review

January/February 2004

(<http://americanpharmaceuticalreview.com/ViewArticle.aspx?ContentID=2>)

"If using an Association of Official Analytical Chemists (AOAC) method, microorganisms specified in the reference which are most likely to be found in the manufacturing environment should be used and tests performed on microbial isolates fre-

(Continued on page 4)



(Continued from page 3)

quently found in the environment can provide additional information on the effectiveness of disinfectants."

Technical Report No. 13: Fundamentals of an Environmental Monitoring Program

Journal of Pharmaceutical Science and Technology, Supplement TR13, Vol. 55, No. 5

Parenteral Drug Association

September/October 2001

"It is a sound practice to perform challenge testing of the selected sanitizers/disinfectants with isolates routinely recovered by the environmental monitoring program. This establishes the practical effectiveness of the disinfectants."

"Pharmaceutical Company Jelfa SA (Poland) Receives Warning Letter (7/14/11) Part II"

Barry A. Friedman, PhD LLC

Blog (<http://barryafriedmanphdllc.wordpress.com/>)

August 15, 2011

"Disinfectant Efficacy Studies should be considered as a fundamental requirement during the development of Qualifications of disinfectants on various surfaces with both ATCC and in-house isolates."

"Control Strategies for Fungal Contamination in Cleanrooms"

Paul Lopolito, Carol Bartnett, Jim Polarine

Controlled Environments Magazine

September 2007

(<http://www.cemag.us/print/669>)

"It is generally recommended to use fungal spore suspensions of both reference cultures and environmental isolates... Regulatory authorities also expect to see the specific environmental isolates most frequently found in the facility included in the disinfectant effectiveness testing."

"Disinfectant Validation"

Darren Wallis, GlaxoSmithKline

American Pharmaceutical Review

[unknown publish date]

(<http://americanpharmaceuticalreview.com/ViewArticle.aspx?ContentID=522>)



"Disinfectant validation involves the documented verification and implementation of procedures that have been shown to achieve adequate control over the range and levels of microorganisms that may be encountered in a facility."

MEDIA GROWTH PROMOTION

In recent years the FDA has cited manufacturers for their lack of inclusion of in-house isolates in media growth promotion.

FDA Warning Letter

CP Pharmaceuticals, Ltd.

October 29, 2010

(<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/ucm233036.htm>)

"...your firm does not perform challenge testing to the sterility media with environmental isolates from the environmental monitoring program."

FDA Warning Letter

Centocor, Inc.

July 10, 1998

(<http://www.fda.gov/downloads/ICECI/EnforcementActions/WarningLetters/1998/UCM066636.pdf>)

"Growth promotion qualification of the media used for environmental monitoring does not include a challenge with mold isolates."

FDA Warning Letter

American Pharmaceutical Partners, Inc.

January 11, 2001

(<http://www.fda.gov/downloads/ICECI/EnforcementActions/WarningLetters/2001/UCM069215.pdf>)

"Growth promotion testing performed on media fill vials does not include evidence the media is capable of detecting environmental isolates found in class 100 filling areas. For example, mold organisms are not used to challenge media, even though mold isolates have been identified in filling room 1."

(Continued on page 7)

Recent Developments in European Regulatory Requirements: Issues Affecting the Microbiologist

Tim Sandle, PhD

Email: tim.sandle@bpl.co.uk

Blog: www.pharmig.blogspot.com

Introduction

This paper surveys some of the recent developments in European Regulatory Requirements that have taken place in 2011. By ‘regulatory developments’ I am referring to the wider definition in terms of pharmacopoeial changes and inspectorate guidelines. Reference is also made to documents issued by influential organisations like the World Health Organisation and ISO. The review of regu-

latory changes is divided into different sections, depending upon the body which issued the change or proposed change. The items selected are those which will be of interest to pharmaceutical microbiologists.

European Pharmacopoeia

The European Pharmacopoeia is revised and issued by the European Directorate for the Quality of Medicines & HealthCare (EDQM). The EDQM (Council of Europe) is a key European Organisation involved in Harmonisation and Co-ordination of Standardisation, Regulation and Quality Control of Medicines, Blood Transfusion, Organ Transplantation, Pharmaceuticals and Pharmaceutical Care. The European Pharmacopoeia was first published in 1967.

The European Pharmacopoeia is published in two volumes. The first volume consists of general chapters (such as the sterility test) and the second of specific monographs for materials (such as sodium heparin). All producers of medicines or substances for pharmaceutical use must apply the quality standards of the European Pharmacopoeia for the marketing and use of these products in Europe.

The 7th edition of the European Pharmacopoeia was published in January 2011. Since then there have been a series of updates which have been issued as supplements.

Recent changes

European Pharmacopoeia: Rapid implementation of revised general chapter 5.2.8

An important European Pharmacopoeia update was the rapid implementation of revised general chapter 5.2.8. The revised general chapter 5.2.8 “Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal

(Continued on page 6)

Accugenix
Discover the Power of
Proteotypic Identifications

**Introducing
AccuPRO-ID™**

**AccuPRO-ID™ - The ideal choice for
routine environmental monitoring and
primary screening of bacterial organisms.**

- Provides 98% Species-level identifications
- Higher accuracy at lower cost to customers currently using phenotypic methods
- Utilizes our validated, cGMP libraries, based on testing hundreds of thousands of industry-relevant organisms

For additional information:
www.accugenix.com
+1.302.292.8888

Identify with
Accugenix

Image: Copyright Dennis Kunkel Microscopy, Inc.



(Continued from page 5)

products” was adopted following a fast-track procedure and is to be implemented on 1 July 2011.

Transmissible Spongiform Encephalopathies (TSEs) are chronic degenerative nervous diseases characterised by the accumulation of an abnormal isoform of a cellular glycoprotein (known as PrP or prion protein).

The new chapter focuses on:

- Control measures
- Selection of starting materials
- Design and control of manufacturing

When manufacturers have a choice the use of materials from ‘non TSE-relevant animal species’ or non-animal origin is preferred.



Proposed changes

In addition to the changes that have taken place, there is one proposed change which falls outside the harmonization program with the USP. This is for the following chapter:

2.6.31. Microbiological examination of herbal medicinal products for oral use - under revision

The European Pharmacopoeia is revising the following microbiology chapter: 2.6.31 Microbiological examination of herbal medicinal products for oral use.

The changes are designed to bring the chapter in close alignment to chapter 2.6.13, specifically:

- The absence test for *E. coli* and the semi-quantitative test for bile-tolerant gram-negative bacteria (probable number method) to become same methods as those currently published in the harmonised chapter 2.6.13.
- The proposed method for Salmonella (test for absence) is similar to the method currently published in chapter 2.6.13 but the proposed method was adapted to the increased sample size (25 g or 25 ml instead of 10 g or 10 ml), shown to be appropriate for herbal medicinal products.
- For herbal medicinal products with naturally high bioburden the use of buffered peptone medium instead of casein soya bean digest broth is proposed because of higher buffer capacity.

A separate chapter is still required because herbal drugs are outside the scope of pharmacopoeial harmonisation.

PIC/S

From 1st January 2011 the FDA became a member of the PIC/S (Pharmaceutical Inspection and Co operation Scheme). Up until this point the PIC/S was primarily a European based regulatory organization.

(Continued on page 11)



Cryologics, Inc.
Specializing in Microbial Cryopreservation

Announcing CryoHC™!

CryoHC™ is custom-manufactured using your in-house microbial isolates. Each 0.1 mL aliquot contains 10^6 to 10^7 cfu, making it ideal for disinfectant efficacy testing, antimicrobial effectiveness testing, and a variety of other applications. We can also custom-manufacture your CryoHC™ product to contain any concentration range you require.

Our pricing is straightforward. There are no fees beyond our published pricing schedule, and we do not require a deposit. Even shipping costs are included. Visit our website for more information.

info@cryologics.com (610) 847-8781
www.cryologics.com

(Continued from page 4)

FDA 483 Observation

McNeil Consumer Healthcare

April 30, 2010

(<http://www.fda.gov/downloads/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/UCM210772.pdf>)

"... the firm does not test TSA...during growth promotion tests for microorganisms to include for example, molds, yeasts and other potential known environmental contaminants found in the manufacturing facility and/or raw materials."

FDA 483 Observation

CSL Biotherapies, Victoria, Australia

May 2008

Growth promotion studies for purchased and in-house growth media were deficient because there was "no inclusion of environmental isolates in the growth promotions that are conducted, including growth promotion studies for aseptic media simulations".

In this regulatory reference, the FDA acknowledges the appropriate use of in-house isolates in growth promotion testing.

BLA Recommendation (FDA)

CSL Behring

January 16, 2009

(<http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/>

[FractionatedPlasmaProducts/ucm162768.htm](http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm162768.htm))

Regarding growth promotion of media used for media fills: "Growth promotion studies were conducted successfully using indicator microorganisms per USP as well as local isolates."

Below are two references to regulatory guidance on use of in-house isolates in growth promotion testing.

Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice

Food and Drug Administration

September 2004

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf>)

"The QC laboratory should determine if USP indicator organisms sufficiently represent production-related isolates. Environmental monitoring and sterility test isolates can be substituted (as appropriate) or added to the growth promotion challenge."

Pharmaceutical Inspection Convention / Pharmaceutical Inspection Cooperation Scheme (PIC/S)

Recommendation on Sterility Testing

25 September 2007

(<http://www.picscheme.org/publication.php?id=8>)

"Growth promotion test: ... Environmental or fastidious organisms may be used if alternative non-

(Continued on page 8)

Regulatory Compliance

It's critical to keep your ducks in a row



Media Solutions for USP <1116> Compliance

With BD Prepared Environmental Monitoring Media, you'll find it a lot easier to stay in line with regulatory compliance.

Microbiology – it's what we do.

Find out what we can do for you. Visit us on the web at www.bd.com/ds



BD, BD Logo and all other trademarks are property of Becton, Dickinson and Company. ©2009 BD

BD Diagnostics
800.638.8663



(Continued from page 7)

selective enrichment media have been selected for the sterility test.”

A recently published PDA Technical report provides guidance.

Technical Report No. 22: Process Simulation for Aseptically Filled Products

Parenteral Drug Association
December 2011

"The growth promotion properties of the incubation media should be evaluated using pharmacopeial methods. The inclusions of tests for environmental organisms or those isolated from sterility test positives are recommended."

"Growth promotion testing ... is performed using pharmacopeial methods. Consideration should be given to testing with other microorganisms found in the aseptic processing area environment, such as those isolated during environmental and personnel monitoring and sterility test contaminants."

The USP offers two compendial references.

USP <1117> Microbiological Best Laboratory Practices

"... microorganisms used in growth-promotion testing may be based on the manufacturer's recommendation for a particular medium, or may include representative environmental isolates (but these latter are not to be construed as compendial requirements)."

USP <1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments

"... for the Growth Promotion test, representative microflora isolated from the controlled environment or ATCC strain preparations of these isolates may also be used to test media."

Prominent industry thought-leaders have addressed the importance of including in-house isolates in media growth promotion.

"Microbial Testing in Support of Aseptic Pro-

cessing"

Anthony M. Cundell
Pharmaceutical Technology
June 2004

"Growth promotion should be demonstrated using organisms listed in USP General Chapter <71> as well as environmental, personnel, and sterility test failure isolates [at the] <100-cfu challenge."

"Quality Control of Microbiological Culture Media"

Scott Sutton, Ph.D.
Pharmaceutical Microbiology Forum Newsletter
Volume 12, Number 1
January, 2006

(<http://www.microbiologyforum.org/PMFNews/PMFNews.12.01.0601.pdf>)

"In addition to the compendial organisms required in the [media growth promotion] tests, addition of specific microorganisms of interest could be useful if they have been recovered from past tests (e.g. a Sterility Test contaminant or a frequent environmental monitoring isolate)."

"Introduction to Sterility Testing: Control of the Environment, Test Limitations, and Investigating Manufacturing Systems"

Deborah E. Mentel, Pfizer Global Research & Development
American Pharmaceutical Review
Jan/Feb 2006

(<http://americanpharmaceuticalreview.com/ViewArticle.aspx?ContentID=335>)

"The media must be challenged with the organisms listed in the current version of the compendia as well as one or more in-house isolates... The in-house cultures used must be qualified as well, with regards to identity and population size. The challenge should be with <100 CFU and the population size must be verified and recorded."

METHOD SUITABILITY/VALIDATION

The FDA recently published a proposed rule that includes the importance of implementing in-house isolates into method validation.

(Continued on page 9)

(Continued from page 8)

Proposed Rule: Amendments to Sterility Test Requirements for Biological Products

Food and Drug Administration
21 CFR Parts 600, 610, and 680
Federal Register. Vol. 76, No. 119.
June 21, 2011

(<http://www.gpo.gov/fdsys/pkg/FR-2011-06-21/pdf/2011-15346.pdf>)

Regarding sterility test method validation: "The test organisms selected should reflect organisms that could be found in the product, process, or manufacturing environment."

Use of in-house isolates in method validation is described in recent industry publications.

"The Use of Environmental Isolates"

Tim Sandle, Ph.D.
Pharmaceutical Microbiology Blog
January 10, 2010

(<http://pharmig.blogspot.com/2010/01/use-of-environmental-isolates.html>)

"There is a strong argument that environmental isolates are the best challenge to media and for validation studies like sterility test validation. They are the most sensitive micro-organisms, having been exposed recently to disinfectants, particular soils etc."

"Bioburden Method Suitability for Cleaning and Sanitation Monitoring: How Far Do We Have to Go?"

Angel L. Salaman-Byron
Pharmaceutical Technology
August 2, 2010

"The author highly suggests performing test method suitability studies using wild-type isolates from production surfaces instead of laboratory-adapted strains of bacteria. Wild-type strains are a better representation of the organisms encountered on production areas than those strains that lack wild characteristics."

RAPID MICROBIAL METHODS

The field of RMMs is a burgeoning area of much discussion and advancement. The FDA provides guidance on the use of in-house isolates in RMM validation.

Guidance for Industry: Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products (Draft)

Food and Drug Administration
Center for Biologics Evaluation and Research
February 2008

(<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072612.htm>)

"You should develop a panel of microorganisms relevant to the product and process to challenge the performance of your RMM. We recommend that you include in your panel microorganisms which represent the following categories:

...

(Continued on page 10)

FLEXIBILITY
Run Both Chromogenic AND
Turbidimetric Assays in
The Same Kinetic Tube Reader

PyrosKinetix
FLEX
Associates of Cape Cod, Inc.

ASSOCIATES OF
CAPE COD
INCORPORATED 888.395.2221
www.acciusa.com



(Continued from page 9)

- isolates detected in starting materials
- isolates detected by in-process testing or during preliminary product testing
- isolates detected by environmental monitoring of your manufacturing facility
- isolates from your production areas which represent low nutrient and high stress environments ... “

The use of in-house isolates in RMM validation is also discussed in industry publications.

"Automated Rapid Microbiological Methods for the Biopharmaceutical Industry: Selection, Validation, and Implementation for an Autologous Cell Therapy Product"

John Duguid & Gary C. du Moulin Ph.D., Quality Systems, Genzyme
American Pharmaceutical Review
[unknown publish date]
(<http://americanpharmaceuticalreview.com/ViewArticle.aspx?ContentID=4037>)

"Validation studies evaluated sterility test samples from primary culture, expansion culture, and final product culture with a microbial challenge comprised of 10 microbial species. These species included a mix of commercial reference strains and stressed cells from frozen archives of environmental isolates and sterility test failures. During the validation process, FDA recommended challenge microorganisms ..."

"The Introduction of Qualitative Rapid Microbiological Methods for Drug-Product Testing"

Paul Newby, Gilberto Dalmaso, Silvano Lonardi, Bryan Riley, Peter Cooney, and Kim Tyndall
Pharmaceutical Technology, Process Analytical Technology
2004

"To demonstrate the [RMM's] ability to detect a range of microorganisms, at least six replicate samples of drug product were spiked with 10 to 100 cfu of microorganisms from site-specific isolates and ... compendial microorganisms ..."

Upcoming PMF Conferences

2012 PMF Open Conference on Compendial Issues – Compendial Guidance in QC Microbiology and CGMP

January 30-31, 2012 Baltimore, MD

<http://www.cvent.com/d/ccq862>

Recent years have seen an increase in USP informational chapters (those with numbers over 1000) that blur the line between Compendial requirements and CGMP for the QC microbiologist. These chapters include the draft <1113> (Microbial ID) <1116> (Cleanrooms), <1117> (Best Lab Practice), <1223> (Validation of Alternate Methods), and <1227> (Microbial Recovery) among others. This year's Open Conference will provide up-to-the-minute, essential information about several of the recent and proposed changes in the Compendia from this perspective.

PMF Conference on Bioburden Contamination Control – Current Thinking on Facility Control for Support of Non-Sterile Manufacturing

February 27-28, 2012 in Key Largo, FL

<http://www.cvent.com/d/4cqkfm>

Recent regulatory actions have underscored the central importance of contamination control to the pharmaceutical, OTC, biologics, dietary supplement and personal-care products industries.

This conference will focus on the GMP of contamination control, with emphasis on regulatory guidance, enforcement activities and good science.

This is the third annual PMF conference on contamination control to be held in the Florida Keys, and like others, it offers participants a unique opportunity to meet in small, interactive sessions with key thought leaders about a very important topic.

PMF Conference on Alternate and Rapid Microbiological Methods – Understanding Industry Perspectives and Regulatory Expectations

March 26-27, 2012 Las Vegas, NV

<http://www.cvent.com/d/hcqk09>

Alternate and rapid microbiological methods are those that provide information currently provided by conventional QC microbiological methods, but do so with at least the accuracy and precision of the traditional methods while providing some measureable advantage, including faster time to result. Such methods have been available for over 40 years, but remain rare in the QC pharmaceutical labs. This conference will explore this apparent contradiction from the regulatory, business and scientific perspectives.

Co-moderated by Michael Miller and Scott Sutton, a wide range of perspectives will be provided to explore this topic.



(Continued from page 6)

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) are two international instruments between countries and pharmaceutical inspection authorities. The PIC/S is meant as an instrument to improve co-operation in the field of Good Manufacturing Practices between regulatory authorities and the pharmaceutical industry. In relation to PIC/S, the remit of the PIC/S is likely to be extended to include GDP (Good Distribution Practice) as well as GMP (Good Manufacturing Practice). A decision will be taken early in 2012.

ISO

Revision of cleanroom standards

The main cleanroom standard: ISO 14644, is undergoing revision and that the drafts were issued for public comment during 2011.

The ISO 14644 standard is made up of a number of parts. The first two parts are being revised, namely:



- ISO 14644-1 Cleanrooms and associated controlled environments: Part 1: Classification of air cleanliness by particle concentration
- ISO 14644-2 Cleanrooms and associated controlled environments: Part 2: Specifications for monitoring and periodic testing to prove continued compliance with ISO 14644-1

The most significant changes being considered are:

- Whether the Upper Confidence Limit calculation and Student 'T' Test are removed.
- If the 'square root rule' for calculating the number of sample locations for classification is removed.
- Consideration of the adoption of a new table for the determination of the number of sample locations for classification according to the size of the area to be classified.
- The addition of a normative reference to ISO 21501-4 which would make compliance with ISO 21501-4 a requirement. ISO 21501-4 provides a calibration procedure and verification method for particle counters used to classify and monitor cleanrooms. ISO 21501 sets out the tests required for the calibration of particle counters. These tests are:

- Size calibration
- Verification of size setting
- Counting efficiency
- Size resolution
- False count rate
- Concentration limit
- Sampling flow rate

(Continued on page 12)




For Outsourced IDs and More

- ✓ We've been identifying microbes for more than 22 years [over 300,000 isolates].
- ✓ Can help you to identify microorganisms utilizing 16S and 28S rDNA gene sequencing or microscopic fungal identifications.
- ✓ Fungal IDs are our Sweet Spot – our staff mycologist, in conjunction with our sequencers and DNA analysis, can differentiate closely related species to give you the definitive answer. Proof is our collaboration with the leader in sequencer technologies. Check out our website for details.
- ✓ We can set up and implement your special project using our microbial expertise.
- ✓ Microcheck is also an A2LA Accredited Proficiency Test Provider

www.microcheck.com

✓ GET MORE MICROCHECK ANSWERS



PHONE: 1-866-709-6600
FAX: 1-866-606-6100
EMAIL: info@microcheck.com

(Continued from page 11)

- Sampling time
- Sampling volume

The only means by which a particle counter used in pharmaceutical grade cleanrooms can be calibrated (where the lowest counted particle size is 0.5 microns) is by using a particle counter which can accurately count as low as 0.3 microns.

Although the standard is a considerable improvement on what has been in place previously, it does pose an obsolescence threat to older models of counter as many will not meet the new standard. This will become a problem for those who need to meet GMP regulations for 2011.

- The Air Cleanliness Classification Table defining the maximum allowable number of particles for each ISO class is likely to be modified. Most significantly to the pharmaceutical and healthcare industries, reference to the number of particles >5.0 micron may be removed for ISO Class 5 areas (this is significant because EU GMP Annex 1 refers to particles 5.0 micron for Grade A conditions and refers to this being equivalent to ISO Class 4.8).

A meeting was held in Milan in October 2011 and the outcome was that the two ISO 14644 parts are to be redrafted and a new DIS (draft international standard) prepared for public comment in 2012.

EMA / EU GMP

Guideline on similar biological medicinal products containing monoclonal antibodies

The EMA have issued a new draft document: "Guideline on similar biological medicinal products containing monoclonal antibodies."

The introduction reads:

"This guideline lays down the non-clinical and clinical requirements for monoclonal antibody (mAb) containing medicinal products claiming to



QC automation
just got greener!

MODA is now a Lonza company.
More science. Less paper.™

Go paperless today!

www.lonza.com/rts

Lonza

be similar to another one already marketed. The non-clinical section addresses the pharmacotoxicological requirements and the clinical section the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as pharmacovigilance aspects."

The draft can be accessed, as a pdf document, here: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf

EU GMP Updates: Chapter 4 (Documentation) and Annex 11 (Computerised Systems)

Chapter 4 (Documentation) and Annex 11

(Continued on page 13)

(Continued from page 12)

(Computerised Systems) have been revised by the European Commission. Both came into operation during 2011.

A summary of the reasons for the changes are

- Annex 11: the Annex has been revised in response to the increased use of computerised systems and complexity of these systems. Consequential amendments have been made to Chapter 4 of the GMP Guide. Revision of the Annex has resulted in a restructuring of the document into the following five areas (and 17 sub-chapters). Principles, General, Project Phase, Operational Phase and Glossary.
- Chapter 4: the sections on 'generation and

control of documentation' and 'retention of documents' have been revised, in light of the increasing use of electronic documents within the GMP environment.

World Health Organization

Virological surveillance of influenza

Here is a new World Health Organization publication of note: 'WHO Manual for the laboratory diagnosis and virological surveillance of influenza'.

In many settings influenza is recognized as a major cause of disease and death. In other parts of the world, however, its epidemiology and the degree of its impact on human health remain relatively uncertain - in large part due to a lack of virological and disease surveillance.

WHO has developed this manual in order to strengthen the laboratory diagnosis and virological surveillance of influenza infection by providing standard methods for the collection, detection, isolation and characterization of viruses.

To find out more: http://www.who.int/csr/disease/influenza/manual_diagnosis_surveillance_influenza/en/index.html

WHO good practices for pharmaceutical microbiology

The World Health Organization (WHO) has issued an important annex to WHO Technical Report Series, No. 961, 2011. This annex is 'Good Practices for Pharmaceutical Microbiology Laboratories'.

The report covers the following important areas:

- Personnel
- Environment
- Premises
- Environmental monitoring in the laboratory



Biotest
From Nature for Life

Microbiology Tests & Services

Solutions for all your Environmental & Product Testing Needs

- heipha Culture Media
- HYCON RCS & LKI (Agar Strips)
- HYCON OKI (Contact Slides)
- Hycon APC
- HSS Hygiene Screening System

Coming Soon...
Pyrogen Detection System MAT

heipha

Biotest Microbiology Corporation • Toll Free: 877.210.5103 • www.BiotestUSA.com

(Continued on page 14)

(Continued from page 13)

- Cleaning, disinfection and hygiene
- Sterility test facilities
- Validation of test methods
- Equipment
- Maintenance of equipment
- Qualification
- Calibration, performance verification and monitoring of use
- Reagents and culture media
- Organism resuscitation
- Reference materials and reference cultures
- International standards and pharmacopoeial reference substances
- Sampling
- Disposal of contaminated waste
- Quality assurance of results and quality control of performance
- Internal quality control

- Testing procedures
- Test reports

The document can be found here: http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex2.pdf

The report appears to cover much of the same ground as the USP chapter <1117>

WHO guide: handling of hazardous or highly-active substances

The World Health Organization (WHO) in June 2010 published a new guide on the handling of hazardous or highly-active substances. This is as an annex to WHO report 957.

The aim of the guide is to:

"These guidelines set out good practices applicable to facilities handling pharmaceutical products (including active pharmaceutical ingredients (APIs)) that contain hazardous substances such as certain hormones, steroids or cytotoxins. They do not replace national legislation for protection of the environment and personnel. Other WHO guides to good manufacturing practices (GMP) and regulations need to be observed in addition to the workers' safety criteria"

The text covers:

1. Introduction
2. General
3. Glossary
4. Risk assessment
5. Product protection
6. Personal protection equipment and breathing air systems
7. Environmental protection
8. Facility layout
9. Air-handling systems
10. Air-handling units
11. Safe change filter housings
12. Personnel decontamination systems
13. Effluent treatment
14. Maintenance

(Continued on page 15)



AEMTEK

Fungal Identification Service and Training

Don't have a mycologist on staff?
Let Aemtek help!

Our team of PhD mycologists specialize in:

- Yeast and mold identification and enumeration
- Training in fungal identification
- Fungal contamination problem-solving
- Antifungal efficacy testing

Phone: 510-979-1979
Email: lab@aemtek.com
Web: www.aemtek.com

(Continued from page 14)

15. Qualification and validation References

The report can be found here: http://whqlibdoc.who.int/trs/WHO_TRS_957_eng.pdf#page=206

European healthcare

New guidance on microbiological examination of healthcare environments

New guidance has been published, in the UK NHS, on the microbiological examination of healthcare environments.

The guidance - for healthcare professionals on the microbiological examination of food, water and environmental samples taken from the healthcare environment – was recently produced by the UK Health Protection Agency Food, Water and Environmental Microbiology Network – was published recently.

The guidance is intended to facilitate investigations aimed at demonstrating that safe environments exist for patients, visitors and staff – summarising relevant legislation and guidance for microbiologists and infection control nurses and providing clarification/guidance on sampling and result interpretation where these are currently lacking from other sources.

In separate sections on food, water, environmental and air sampling, appropriate procedures and equipment essential for sampling, analysis and meaningful interpretation of test results are described.

To access the guide (free to view) go here: <http://www.hpa.org.uk/Publications/InfectiousDiseases/LaboratoryReferences/1012examiningFWEsamples/>

Summary

This paper has reviewed some of the regulatory changes within Europe and from WHO and ISO

which will be of interest to pharmaceutical microbiologists, even if this is as an aside to core laboratory work. In undertaking this review it is clear that the gradual process of harmonization with North American continues (between pharmacopeia and with the FDA joining the PIC/S), although several differences remain.



About the Author:

Dr. Tim Sandle is the Head of Microbiology at Bio Products Laboratory Limited. In addition, Dr. Sandle is an honorary consultant with the School of Pharmacy and Pharmaceutical Sciences, University of Manchester and is a tutor for the university's pharmaceutical microbiology MS course. Dr. Sandle serves on several committees relating to pharmaceutical microbiology and cleanroom contamination control including BSI cleanroom standards and the UK Pharmaceutical Microbiology Interest Group. Dr. Sandle has written over one hundred papers, book chapters and technical articles and he also runs an on-line microbiology blog (www.pharmig.blogspot.com).

BioBall™
Quantitative QC Made Easy!

NOW AVAILABLE!

Plant Isolates manufactured into BioBall format!

- Plant Isolate is any strain from your manufacturing environment that is not a culture collection strain
- Single dose product – 60 cfu
- Precise known number of cfu

For more information please visit www.biomerieux-industry.com/bioball

BIOMÉRIEUX
INDUSTRY



Upcoming Events

PMF Open Conference on Compendial Issues - Compendial Guidance in QC Microbiology and CGMP

January 30-31, 2012 - Baltimore, MD

<http://www.cvent.com/d/ccq862>

PMF Conference on Bioburden Contamination Control – Current Thinking on Facility Control for Support of Non-Sterile Manufacturing

February 27-28, 2012 - Key Largo, FL

<http://www.cvent.com/d/4cqkfm>

PMF Conference on Alternate and Rapid Microbiological Methods – Understanding Industry Perspectives and Regulatory Expectations

March 26-27, 2012 - Las Vegas, NV

<http://www.cvent.com/d/hcqk09>

PMF Conference on Environmental Monitoring - EM for Cleanrooms and Controlled Environments – Industry standards, Regulatory requirements, Product Quality Requirements

April 23-24, 2012 - San Francisco, CA

http://microbiologyforum.org/2012/HPA1204_Interest.html

PMF Conference on Microbiological Laboratory Investigations

May 21-22, 2012 - Philadelphia, PA

http://microbiologyforum.org/2012/HPA1205_Interest.html

PMF Bacterial Endotoxin Summit – “Interference in the BET”

September 17-18, 2012 - San Francisco, CA

http://microbiologyforum.org/2012/HPA1206_Interest.html

PMF Fall Forum – Leading the Modern QC Microbiology Lab

October 15-16, 2012 - Philadelphia, PA

http://microbiologyforum.org/2012/HPA1207_Interest.html

PMF Conference – Validation Concerns in the QC Microbiology Lab

November 8-9, 2012 - Dallas-Ft. Worth Metroplex, TX

http://microbiologyforum.org/2012/HPA1208_Interest.html

Full Listing at

<http://www.microbiologyforum.org/upcoming.htm>



USP Corner

Any questions concerning USP documents should be sent to Radhakrishna (Radha) Tirumalai, Ph.D. You can reach Dr. Tirumalai at: (706) 353-4514, via mail at United States Pharmacopeia, 126 Twinbrook Parkway, Rockville, MD 20852 or via e-mail at RST@USP.org. You can write representing your company, or as an individual scientist.

The *Pharmacopeial Forum* is now available for free online at <http://www.usp.org/USPNF/pf/>

Discussion List Update

PMFList:

Number of Subscribers: 4349

Number of Countries: 64

Number of Messages Last Month: 168

PSDGList (Pharma Stability Discussion Group):

Number of Subscribers: 1576

Number of Countries: 35

C-CEList (Cleanrooms and Controlled Environments

Number of Subscribers: 809

Number of Countries: 25

Membership is **FREE**. To join the PMFList (or any of the other lists, as well), visit

<http://www.microbiol.org/email-discussion-lists/pmflist/>
and register.

You can ask, answer, or read questions and comments from your colleagues. Archives of the lists are available at:

<http://www.microbiol.org/email-discussion-lists/pmflist/>
<http://www.microbiol.org/email-discussion-lists/psdglis/>
<http://www.microbiol.org/email-discussion-lists/c-celist/>