

ASEPTIC PROCESSING 2005

March 31-April 1, 2005 • Park Hyatt • Philadelphia, PA

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The New FDA Guidance, and Implementing Technologies to Meet Evolving Standards in the Aseptic Manufacturing Environment

March 31-April 1, 2005 • Park Hyatt • Philadelphia, PA

Inclusive Pre-Conference Workshop, Thursday, March 31, 2005

Clarifying the New FDA Guidance: “Sterile Drug Products Produced by Aseptic Processing”

*Les Edwards, Partner/Principal Engineer, Advanced Barrier Process, LLC
Austin McDonald, Senior Engineer and Partner, GL Engineering*

Hear from Industry Leaders in the Areas of Global Harmonization, Environmental Monitoring, Avoiding 483 Citations, Designing Cleanrooms, Outsourcing to CMOs, Isolator Technologies, Lyophilization, and More!

- Explore the Scope, Technical Requirements, and Controversial Aspects of the New Aseptic Processing Guidance
- Prepare for FDA Inspections – Avoiding 483s, Warning Letters, and Product Recalls
- Explore Antimicrobial Regulations, Technologies, and Applications for Cleanrooms
- Achieve Harmonization of FDA, EMEA, ISO, and WHO Aseptic Requirements
- Improve and Maintain Aseptic Transfer Techniques
- Maintain Sterility and Prevent Cross-Contamination in the Lyophilization Process
- Pinpoint New Solutions and Techniques in Isolation Technology

FOCUS ON LYOPHILIZATION

Clinical Scale Isolator-Based Aseptic Production of Liquid and Lyophilized Products

Sterility Issues for the Lyophilization Process

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Inclusive Pre-Conference Workshop, Thursday, March 31, 2005

Clarifying the New FDA Guidance: “Sterile Drug Products Produced by Aseptic Processing”

8:30 *Conference Registration and Coffee*

9:00 *Workshop Begins*

In September of 2004, FDA published its finalized guidance on Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. This long-awaited guidance is profoundly affecting aseptic processing activities across the industry. The guidance introduces a number of new “requirements” for aseptic processing, which will potentially alter operating practices. This workshop session will review the rationale behind the guidance creation, the differing views of the document, and most importantly its impact on operations. This in-depth session is a critical review of FDA’s guidance and the implications for compliance. Learning objectives include:

- Recognizing the more controversial aspects of the FDA’s aseptic processing guidance
- Understanding the FDA’s rationale and focus for new guidance
- Identifying potential impact on aseptic processing operating practices

About the Workshop Leaders

Les Edwards is Partner/Principal Engineer of Advanced Barrier Process, LLC, a technical services/consulting firm focusing upon cGMP project support for conventional and isolated aseptic processing projects including specification through validation of process equipment and isolator systems, including potent compound applications. Prior to co-founding Advanced Barrier Concepts Inc. in 1994, Mr. Edwards was contracted at Merck (West Point, PA) providing project guidance and technical expertise for isolation projects. His prior experience includes research and development work on hydrogen peroxide gas sanitization systems (STERIS, formerly AMSCO) plus management positions in biomedical engineering. Mr. Edwards holds an undergraduate degree in Bioengineering and a master’s degree in Technology Management, both from the University of Pennsylvania in Philadelphia, PA. He has spoken at numerous conferences on isolation technology, hydrogen peroxide sterilization, and aseptic processing.

Austin McDonald is a Senior Engineer and Partner at GL Engineering, an equipment integrator and provider of skilled engineering resources to the pharmaceutical industry, supporting clients with the design, procurement, testing, and facility integration of sterile processing, packaging, and containment equipment. With extensive experience implementing sterile processes in Europe and the United States, Austin’s specialist areas are sterilization, sterile component handling, sterile filling of vials and syringes, lyophilization, lyophilizer loading systems, automated inspection systems and the handling of complex materials including, cytotoxic substances, carcinogenic substances, biological hazards, and radioactive pharmaceuticals. Prior to co-founding GL Engineering, he was Director of Barrier Technology at Kvaerner Process, Bridgewater, NJ, and a Director at the Tanshire Group, Elstead, Surrey, UK (now Bovis Lend Lease). He has spoken at numerous conferences on sterile processing and isolation technology, and has written on many aspects affecting the integration of isolator systems with sterile processes.

12:00 *Luncheon*

1:00 *Chairperson’s Welcome and Opening Remarks*

Les Edwards, Partner/Principal Engineer, Advanced Barrier Process, LLC

1:15 **Preparing for FDA Inspections, and Avoiding 483 Citations, Warning Letters, and Product Recalls**

Anthony Cundell, Consultant, former Director of Microbiological Development at Wyeth

Beginning in fiscal year 2005, as part of the FDA CGMPs for the 21st Century Initiative first announced in August 2001, the FDA will pilot a risk-based inspection model for prioritizing drug manufacturing establishments for routine inspection. The risk-ranking model for the list of manufacturing sites identified for inspection include:

- Sites not inspected recently (or ever)
- Sites having a high volume of production
- Sites with a history of significant violations
- Sites making products with a high frequency of recall
- Sites using processes expected to have a greater potential for cross-contamination and/or loss of a state of control
- Sites making sterile and/or prescription drugs

Clearly this will mean continued emphasis on the inspection of plants manufacturing sterile drug products. The speaker will discuss strategies useful in ensuring satisfactory outcomes to regulatory inspections. These include preparing for inspections, meeting past regulatory commitments, managing laboratory and manufacturing investigations, maintaining a high level of compliance, repositioning your aseptic processing operations in response to the 2004 FDA Aseptic Processing Guide, and learning from the regulatory citations of other companies. Patterns in product recall, and warning letters will be presented. The lessons learned from some notable regulatory actions will be outlined.

2:45

Designing and Implementing an Effective Cleaning and Disinfection Program

Jim Polarine, Jr., MA, Technical Service Specialist, STERIS Corp.

This presentation will provide a background on antimicrobial regulations, technologies, and applications for cleanrooms. Additionally, key areas of disinfectant and sterilant chemistries and applications will be addressed. Common questions about the use of antimicrobial products in cleanrooms will be covered.

- Learn the most common chemistries used in cleanrooms
- Review “real world” examples of antimicrobial applications
- Learn how to develop an effective disinfection program
- Learn how to develop disinfectant validation studies
- Understand regulations affecting the use of antimicrobial products in cleanrooms

3:30 *Refreshment Break*

3:45

Identification of Microorganisms Using Comparative DNA Sequencing

Michael Waddington, Vice-President of Laboratory Operations, Accugenix

The FDA has recently released new guidance for the aseptic processing of sterile drugs. Within this document, the FDA has stressed the importance of an environmental monitoring program as one of the most important laboratory controls. The accurate identification and characterization of microorganisms is an essential part of a comprehensive environmental monitoring program. The ability to reproducibly identify microorganisms or track unidentifiable microorganisms is greatly enhanced through the use of molecular methods. This talk will discuss the use of molecular methods, specifically DNA sequencing, with respect to the FDA’s guidance. Theory, practical applications, and case studies will be covered.

4:30

HVAC and Laminar Flow Design and Qualifications

Hardeep Gahunia, PE, Director of Mechanical Engineering, TCPI

In aseptic processing areas that directly impact the quality of the product, HVAC system design is critical to provide certain environment and contamination control in which the manufacturing operations occur. Optimization of HVAC design plays a crucial role, and the following points should be considered for the system to be GMP compliant. The HVAC system must be designed to address these points and meet the financial constraints of the project. Documentation of the design must be sufficient to support commissioning, startup, IQ/OQ, and validation of the system. Points to consider include:

- User requirement specifications
- Process, material, and personal flows
- Environmental design criteria
- System design considerations
 - Maintainability
 - Cleanability
 - Accessibility
 - Flexibility
 - Expandability
 - Reliability

5:15

Close of Day One

Managing Outsourced Aseptic Processing

2:00 **Outsourcing Your Aseptic Processing to a Contract Manufacturing Organization**

Douglas Stockdale, President, Stockdale and Associates

This 45-minute presentation will take the conference attendees through all of the steps for outsourcing their aseptic filling process. Aseptic fill/finish is a very complicated process for a sterile medicine and requires careful consideration for each step of the process.

- Ensure that your organization should be outsourcing aseptic processing
- Develop your requirements to prepare for your request for proposal (RFP)
- Ensure that you are choosing the right partnership
- Prepare an audit specific for aseptic processing
- Identify the necessary steps to complete the technology transfer
- Manage a successful aseptic processing CMO relationship

Friday, April 1, 2005

8:30 *Chairperson's Opening Remarks*
Les Edwards, Partner/Principal Engineer, Advanced Barrier Process, LLC

Achieving International Harmonization

8:45 **Are We Near Harmonization of Environmental Regulatory Standards for Aseptic Processing?**
Gordon Farquharson, Principal Consultant, Bovis Lend Lease Life Science & Pharmaceutical Division, UK
 2004 saw the eventual publication of FDA's final Aseptic Processing Guidance. Many firms, hoping that at last there would be one even playing field, find themselves still confused by the varying requirements expressed in FDA, EMEA, and ISO Standards. This session will quickly review the status of the guidance and then compare and contrast the different requirements. It will also try to establish a set of "Most Demanding Requirements" for those that need to satisfy an international marketplace for their products. The key issues will be highlighted by case experience. Specifically:

- Review of the ISO TC 209 family of standards, and ISO 14644-1:1999 in particular
- The status and requirements of FDA's September 2004 Aseptic Processing Guidance
- The status and latest update information on Annex 1 of the EU GMP from the EMEA
- The status of PIC-s and WHO GMPs
- Consideration and comparison of the critical parameters - airborne particle control and monitoring, bio-contamination, unidirectional airflow, air-change rates, and HEPA filter specifications and testing
- Commentary on practical issues of media simulation

9:30 **Three Key Developments in Hydrogen Peroxide Bio-Decontamination Technology**
James Drinkwater, Process and Validation Director, BIOQUELL Ltd.
 The state-of-the-art in gas concentration sensors, having calibration, accuracy, and response issues, has meant they cannot be used for process control of gassing cycles and must be restricted to use as a monitor. One other physical parameter that has become key to one type of hydrogen peroxide gassing process is dew point and the subsequent micro-condensation formed. Instruments have been developed to measure and control this physical state, making it possible to parametrically control gassing cycles in support of the process analytical technology initiative. Advances in the understanding of the science of the sporicidal gassing process has led to the opportunity to optimize every phase of a gassing cycle to achieve rapid 15-minute gassing during process transfers. With short transfer times, the in-process gassing is brought into the main process flow, eliminating offline multiple batch gassing transfer tasks and bringing back simplicity and flexibility with a saving cost. Maintaining microbial contamination control by barrier technology has long been established. The physical barrier may be material, as found with an isolator, but a combination of material and aerodynamics can also produce a very high level of protection. With RABs comes simplicity as the return air capture and ducting is eliminated from the design. Maintaining aseptic transfer techniques through the RABs barrier can still be maintained, but to compromise the bio-decontamination process by returning to "Wet and Wipe" disinfection may be undesirable. Solutions for sporicidal gassing of RABs systems have been developed and implemented, making these systems a real choice for aseptic processing operations.

- Parametric control of gassing cycles, implementation of PAT
- Another rapid technology development: rapid gassing process transfers – the (15) minute total cycle time (gassing and aeration) for "just in time" delivery of aseptic supplies to critical areas
- Gasable Restricted Access Barriers (RABs) – open or closed systems

10:15 *Refreshment Break*

10:30 **E-Beam Tunnels for Inserting Syringes into a Filling Machine**
Theo Sadat, PhD, Adviser, Linac Technologies
 This presentation introduces the use of electron beam in the insertion of high volumes of syringes to a filling machine or isolator. A sterile transfer unit using 3 low energy electron beam generators is used to decontaminate the surface of tubs containing pre-sterilized syringes in the nest entering a fully automatic filling line housed in an isolator. The system provides 25 kGy minimum irradiation dose on all points of the tub surface, but no significant dose inside the tub itself. Treatment is continuous and rapid, decontaminating up to 6 tubs per minute, i.e., up to 36,000 syringes per hour. It leaves no residue, and is well accepted by operators. The advantages of electron beam technology, which include computer monitoring of sterilization treatment, lack of residues, high continuous throughput, validation, and operating costs, will be discussed.

11:15 **Progresses and New Findings in the Barrier/Isolation Technology for Aseptic Processing**
Dr. Paul Ruffieux, Board Member, SKAN AG
 Different findings will be highlighted as new solutions to improve isolation technology. New scientific data will be presented and discussed. Based on this, an

optimized test method will be presented. A second critical point is the transfer systems and the question, "Is it possible to transfer microorganisms into an isolator through transfer systems?" Actual findings will be demonstrated and solutions will be discussed. Air speed in an isolator is always a discussion. The basic guidelines in US and in the EU propose different solutions. Practical experiments with different air speeds and vide filmed with smoke tests are showing interesting results for different types of isolators. All of these findings will be discussed in addition to different types of isolators for different applications like aseptic/sterile or aseptic/sterile/toxic.

12:00 *Lunch Break*

Focus on Lyophilization

1:00 **Sterility Issues for the Lyophilization Process**
Narlin B. Beaty, PhD, Principal, Qualification Process Solutions, LLC
 Lyophilization encompasses a collection of events, which normally include substantial human involvement as well as time-sensitive and time-consuming processes. An overview of these events will be presented with emphasis to those areas that have chronically resulted in regulatory observations. The two main issues are maintenance of sterility and prevention of cross-contamination. Because lyophilizers are dependent on multiple large-scale systems for their function, each system must be addressed to determine its potential to adversely affect the aseptic environment. Solutions to example events will be considered.

- Process gas filtration
- Overcoming chamber design
- Big doors
- Cleaning, or the lack thereof
- Leaks
- Media fills

1:45 **Clinical Scale Isolator-Based Aseptic Production of Liquid and Lyophilized Products – A Case Study**
Dr. Frank DeSantis, Executive Director, Quintiles
 An overview of the technical capabilities of the processing equipment and facilities will be presented, along with a review of our experience in project management and validation of isolators and allied equipment. Engineering and validation challenges confronted during the course of the project will be covered. The facility is designed to produce clinical supplies of sterile products primarily for use in Phase I and II clinical studies. The clinical filling system consists of a network of stationary isolators each interfaced with a single piece of equipment, as well as two transfer isolators to aseptically transfer components (depyrogenated containers) and/or exposed product (partially stoppered vials) between the stationary isolators. The filling isolator contains a monoblock filler with the capability of handling vials and ampoules over a range of 2-25mL fill volumes. The isolators, located in an ISO Class 8 environment, provide the ISO Class 5 environment during critical phases of production. In addition to the isolators, the system has a dedicated filtration skid with CIP/SIP capability for delivery of sterile liquids to the filling machine. The production facility also includes an autoclave, which can be used for terminal sterilization of products that are heat stable.

2:30 **The Future "State of the Art" for Aseptically Processing Freeze-Dried Products**
Christopher Betterly, Associate, W. L. Gore & Associates
 This presentation focuses on the application of expanded-PTFE microporous membrane to contain and protect parenteral products throughout the lyophilization process. Aseptically transferring and freeze-drying of partially stoppered vials is one of the riskiest operations in pharmaceutical processing. This presentation introduces and describes a new innovative technology, The Gore Product Isolator, and the potential implications of adopting this technology in an aseptic manufacturing environment that could enable firms to effectively increase protection for both their work force and their patients, meet new regulations, and increase operational flexibility.

3:15 **Building Quality and Validation into Engineered Systems: A Modified GAMP4 Methodology for Advanced Aseptic Process Equipment**
Les Edwards, Partner/Principal Engineer, Advanced Barrier Process, LLC
 Key major pharmaceutical manufacturers and equipment vendors are now applying the GAMP4 (Good Automation Manufacturing Practices) not just to computerized control systems, but also to specifying, building, testing, and validating mechanical engineered systems. The concept of "traceability" and early involvement of users and quality into the development and testing of these systems has paid huge dividends in cost control, scheduled maintenance, and well-documented and validatable systems. The basic concept will be outlined, then discussed in practical terms based upon the experiences of a number of pharmaceutical manufacturers and vendors.

4:00 *Close of Conference*

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