PDA Southeast Chapter

May, 2002

SOUTHEAST CHAPTER
www.pdase.org

Letter From the President

I would like to introduce myself. My name is Mary Carver and I am the newly elected President of the PDA Southeast Chapter. I became involved with the chapter shortly after it was formed and served in the capacities of Membership Chairman and Vice President before running for president in the elections last fall. The other officers elected for a two year term include Lisa Eklund (Vice President), Tony Pavell (Treasurer), and Kim Hughes (Secretary).

My objectives for the term are to provide the membership with programs of interest and to increase membership participation in the chapter. Upgrading the website to provide information to the membership is also a high priority. Ultimately we hope to use the website as a convenient way to register for chapter meetings and events in addition to dissemination of information.

My objectives for the term are to provide the membership with programs of interest and to increase membership participation in the chapter.

The charter for the Southeast Chapter of the PDA was issued in September 1997. Since that time the chapter has grown from a few members to more than 1750 members. The chapter has provided educational and networking opportunities to its members since 1997. The success of the chapter has been due to former presidents Terri Polson and Bill Jones, the other officers and committee chairs who have devoted much time and effort to the chapter. I would like to express my personal thanks to all those people for making the Southeast Chapter such a great organization. In addition, I would like to express my thanks to the vendors who have continuously supported the chapter through sponsorship of the meetings, the newsletter, and the website. Thanks also go to all the members who have supported the organization by attending the events.

Future activities currently planned for 2002 include our second annual golf outing on June 14, 2002 and our Fall Vendor Show scheduled for October 24, 2002. Information about these events is included in this newsletter or will be posted on the website at www.pdase.org. I hope to see you all there.

Finally, I would like to ask for feedback from the membership on what type of programs you would like the chapter to provide. It is your chapter, so let us know what you would like us to support. Volunteers are also needed. The chapter functions through the support of volunteers and there is much to do to provide quality programs. We could use your help. If you would like information about committees or you would like to serve as a committee chair or member, please contact me at 919-474-2149 or at mary_carver@eisai.com.

Lisa Eklund, Theresa Frisone, Susan Moore, Mary Carver, Jim Rickloff, Tony Pavell, Cindy Smith, Kim Hughes, Terri Polson

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Containment of Potent Compounds

Presented by Scott Sobolewski, President, Engineered Process Equipment Corp.

Written by James R. Rickloff, Chair, Isolator Users Group

Scott Sobolewski, President of Engineered Process Equipment Corp. out of Charlotte, provided an overview on the issues involved with developing a containment strategy and gave several examples of equipment that is currently available to implement it. Scott explained that a containment strategy groups the likely type of engineering control systems, benchmarks the training requirements according to risk, and categorizes maintenance and cleaning requirements. A thorough risk assessment matrix is then developed to rate the level of operator exposure based on toxicity, dustiness, the quantity of material involved, and the duration of the task. Finally, a selection pyramid can be developed to help arrive at the type of equipment needed to accomplish that task in a safe and reliable manner. This can range from the installation of a good HVAC system to fully automated robotics in isolators.

Several examples of equipment were shared with the audience as a means to educate them on what is considered "state of the art" in the pharmaceutical industry in terms of potent compound manufacturing, loading, and dispensing. Both vertical and horizontal laminar flow containment booths were reviewed along with specialty isolators from Carlisle Barrier Systems that can provide containment for operator exposure levels of under one (1) gram.

Over the past 12 months, the Isolator Users Group has provided topics on high-speed production isolator systems, the decontamination of sterility test materials, and now on the containment of potent compounds. Please forward your suggestions on future topics related to isolation technology to james_rickloff@advancedbarrier.com and every effort will be made to provide a presentation and/or round table discussion at an upcoming chapter meeting.

Microbiological Considerations For the Manufacture and Testing of Non-Sterile Inhaled Products

Written by Betsy Sawyer, Senior Investigator, GlaxoSmithKline

The article below is reprinted from the December 2001 newsletter. A section of the article was inadvertently omitted in the original publication.

The PDA Southeast Chapter Executive Committee extends an apology to the author.

Pharmaceutical inhalation products, dry powdered inhalers (DPIs) and pressurized metered dose inhalers (MDIs) formulated with propellants, pose unique challenges for the microbiologist. In this article, microbiological considerations for their formulation, manufacture, and release testing will be presented. Current trends in microbiological requirements for inhalation products will be discussed.

DPIs and MDIs are usually manufactured in a non-sterile environment. DPI formulations typically contain lactose as the primary excipient and MDIs are formulated with at least 99% propellant with few exceptions. Typical propellants are nonchlorofluorocarbon P134a, and the propellants trichlorofluoromethane (P11) and dichlorodifluoromethane (P12). When compared to other non-sterile products, MDI formulations have unique properties that make them anti-microbial:

- Low water content and activity; desiccating to microorganisms
- **Limited food source for microorganisms**
- Propellant creates anaerobic (no air) conditions
- High pressure

Additionally, microorganisms can die from the "shearing" action when the pressurized product is expelled from the device. Despite the harsh conditions for microorganism survival, there are microorganisms that can survive this environment, like spores of *Bacillus* and mold. Studies support that the propellants have anti-microbial properties, with spores being the only survivors, so there is a low risk of microbial contamination.[1] The studies show that the majority of spores will die over time. When compared to MDIs, the DPIs have the greater risk of being contaminated with microorganisms because lactose, the primary excipient, is naturally occurring so would therefore have more potential for microbial contamination than synthetically derived excipients. The low water activity of the dry powder inhibits microbial survival or proliferation, but lactose is a possible breeding ground for microorganisms if much water is introduced.

There have been cases of inhaled product microbial contamination in the 1990s that led to product recalls and court cases, but they were aqueous inhaled products and not the typical propellant-based products (MDIs) or dry powdered inhalation products.[2,3] The result was heightened awareness of the potential for patient illness from grossly contaminated inhalers and increased scrutiny of manufacturing processes for both aqueous and non-aqueous inhalation products.

Where should microbiological quality be monitored in the manufacture of non-sterile inhalation products?

As with other non-sterile products, microbiological monitoring of raw materials, device components, and routine environmental monitoring should be performed. When setting numerical limits for raw materials, components, and product contact monitoring, the release specification has to be considered. Inhalation products have lower numerical specifications than some of the other non-sterile products and will be discussed later in this article.

The raw materials for the formulation should be monitored for total count and for specific microorganisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella* species. Methodology is presented in USP <61> "Microbial Limit Test," and in European Pharmacopoeia chapters 2.6.12 and 2.6.13. Common MDI excipients include surfactants such as oleic acid and lecithin, which could

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Quality Systems Inspections: The New Drug Compliance Inspection Program

Presented by Mr. Ballard Graham, FDA, District Director, Atlanta
Written by Tony Pavell, Treasurer

Introduction

The new drug inspection compliance program began as a medical device industry inspection program. Based on the program's success within the medical device field, the program has been adapted for the drug industry. The program adaptation for the drug industry began as a pilot study. The pilot compliance program was conducted from January 1, 2001 through June 30, 2001 in six U.S. districts and several foreign inspections. The U.S. districts used in the pilot study included Philadelphia, San Juan, New Jersey, New York, Los Angeles and Dallas.

The pilot compliance program was evaluated using a scale of 1 (strongly disagree) to 5 (strongly agree) for ease/clarity, sufficiency, focus and efficiency by the field investigators, supervisors and compliance officers. The field investigators and supervisors rated the program at greater than 75% in all categories while the compliance officers were a little tougher in their ratings. The compliance officers rated three of their categories around 70% and the review category at 90%. The pilot program concluded with no fatal flaws in 155 inspections. It was well received by the field force as more efficient and more focused. "This meets the program intent to improve the focus and efficiency of the agency due to decreased resources," said Director Graham. The program results were reported to the Field Drug Committee in January 2002 for nationwide implementation of the drug inspection compliance program on February 2, 2002.

The new drug inspection compliance program is essentially a revision to the existing inspection program, offering the following advantages:

- A more systematic approach to drug establishment inspections (EIs)
- Improved efficiency in processing regulatory actions
- Improved organization of 483s
- Improved organization of EI reports
- Assurance of updates to profile classes

The revisions have also resulted in some differences from the old system, including a more systems-oriented inspection approach and an inspection of a minimum number of systems to provide a basis for an overall cGMP compliance decision.

Areas of Program Focus

The program has been organized to focus on the following six systems within a company:

- Quality system
- Facilities and equipment system
- Materials system
- Production system
- Packaging and labeling system
- Laboratory control system

These six systems have many common elements related to the GMPs. They all should have written and approved procedures, adherence to which can be verified through company operations. They all result in documentation that can be reviewed. Additionally, the systems are not limited to finished products; they may include starting and in-process materials. The similarities of the systems lend themselves well to a systematic inspection approach, providing a link to the major systems for inspectional coverage and the assessment of data collected to identify quality problems within any system.

Inspectional Coverage Options

The FDA has three options for inspectional coverage of a facility:

Full inspection

The full inspection option is used for an initial inspection situation for a new company. The full inspection is also used for significant changes like a new product, new potential for cross contamination (new product on an existing line), new technologies/ equipment, a poor compliance history or follow up to a warning letter. The full inspection option involves the investigation of the quality system plus three other systems as part of the FDA visit.

Abbreviated inspection

The abbreviated inspection option is used for surveillance inspections. This inspection option is considered adequate for routine coverage and satisfies the biennial inspectional requirement for GMP inspections. The abbreviated inspection option involves the investigation of the quality system plus one other system as part of the FDA visit. The other system chosen for inspection will be changed for each inspection with district monitoring and is based on observations made during previous inspections. The observation notes used to select the system to inspect may not have been documented as an official observation (483) but may be part of the inspector's general notes contained in the company file.

Compliance inspection

The compliance inspection option is used by the FDA to verify correction of previous deficiencies or as a "for cause" inspection.

The system coverage and inspection detail used with each inspection option is the same. The system coverage is sufficiently detailed, with specific examples selected, to reflect a state of control for every drug profile manufactured by a company.

Importance of Operating Under a State of Control

Operating under a state of control produces finished drug products for which there is an adequate level of assurance of quality, strength, identity and purity. "If any one system is out of control this means the firm is out of control," said Director Graham as the take home message from his presentation.

If a company is classified as out of control using the new program it will result in regulatory action and follow up. The regulatory action may include the full inspection option for the next visit, a warning letter, seizure or injunction. The regulatory follow up will be enacted once the compliance division concurs that the company has an Official Action Indicated (OAI) situation. The OAI situation results in an unacceptable profile of all drug profile classes for a company. This ability to affect all drug profile classes has several significant advantages for the FDA:

1. The FDA spends less time in the plant,, allowing for other company inspections to occur.
2. Placing all profile classes as unacceptable represents a significant compliance tool in that nothing new will be approved for a company until the OAI situation is corrected.
3. The FDA is prevented from becoming the firm's QA program, an advantage because providing QA services for a firm can be a significant resource drain for the FDA.

Common Critical Deficiencies

Critical deficiencies were then presented for each of the program' six focus areas. Many of the deficiencies cited were similar among all of the systems. The most common deficiencies included:

Failure to establish and follow a control system for implementing changes

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Process Equipment for the Pharmaceutical Industry Manufactured from Fully Fluorinated Polymers

Presented by Lew Crenshaw, Marketing Development Leader, E. I. duPont de Nemours and Co.

Written by Kim Hughes, Secretary

Fuoropolymers offer distinct advantages over hydrocarbons, chlorinated polymers (i.e. PVC), and stainless steel in that fluorinated polymers 1) are more inert to chemical attack, 2) have a non-reactive surface, 3) can be used over a wide range of temperature, 4) are non-wetting and non-stick, and 5) are higher purity. These characteristics make this material optimal for fluid handling processes. Fluoropolymers are widely used in the pharmaceutical industry for transfer lines, gaskets, seals, and lining of process vessels. Recently, the material has been used in sanitary piping process systems. In this application, the material is cGMP compliant and comparable in cost to stainless steel. Studies performed with Teflon® PFA, a fluorinated polymer, indicate that the material has very low leachable materials and low absorption. The "cleanability" of this polymer also makes this a suitable material for water and bio-pharm systems in that percent biofilm removal scored >98% in comparison to stainless steel with a removal percentage of 25 – 67%. Fluorinated polymers have traditionally been used in bulk pharma processing. New applications include fermentation and filling equipment and process systems (i.e. bio-pharm systems).

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be tested to establish historical data and vendor certification. As discussed previously, the propellants are so harsh to microorganisms that routine testing is not advisable. For DPIs, lactose is the raw material commonly used, and typically comprises the majority of the formulation. Because it is naturally occurring and it is a possible microorganism foodsource, the lactose should be tested routinely. In addition to microbial limits, the FDA is now requiring that the lactose be tested for endotoxin because it is potentially harmful to lung surfaces. This requirement was introduced several years ago in the 1998 draft FDA document, "Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products." For qualified vendors, historical data and periodic testing thereafter may suffice.

Device components such as cans, actuators, and product contact plastic parts on DPIs should be tested for microbial quality. Establishing baseline counts as part of vendor certification may be sufficient to justify periodic monitoring instead of routine.

Microbiological environmental monitoring should be performed on product contact surfaces, air, and equipment parts that could contribute to the product microbial load. If compressed air is used, it should be periodically monitored for microbial quality. Purified water used for equipment cleaning should be monitored for counts, as well as the presence of potential pathogens. Equipment should be cleaned with 70% isopropyl alcohol or other approved sanitizer. As for all GMP processes, the operators should be trained in microbiological control.

Microbial Limit Testing of Finished Product

DPIs and MDIs should be tested as described in USP <61> "Microbial Limit Test," and in European Pharmacopoeia chapters 2.6.12 and 2.6.13. Developing the test methodology is certainly more challenging than for other non-sterile products because of the manipulations involved in obtaining samples.

DPI Testing

Both the European and U.S. pharmacopoeia state to test 10 cans or 10 grams or milliliters. If the powder is packaged in blister doses, then hundreds of powder doses from blisters would have to be aseptically removed to obtain 10 grams. Lower sample weights may be justified, but even with lower sample sizes, there is still considerably more manipulation in sample removal than for other non-sterile dosage forms. The additional manipulation required to remove the blister contents increases the chances of laboratory contamination into the sample.

MDI Testing (pressurised aerosol products)

The combination of the product formulation, high internal pressure, and complexity of the metering valve make the prospect of aseptically assessing the product a daunting one for the microbiologist. There are several methodologies that can be used to test the can contents:

- The can contents can be chilled to reduce internal pressure, thus permitting the analyst to cut open the can and remove liquid samples. The liquid has to be removed quickly, before it warms up and returns to the vaporous state. The cold liquid will often splatter when touching warm objects.

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con't from page 3, Quality Systems Inspections

- Failure to review and approve procedures
- Failure to qualify computers

Director Graham said, "…the agency has noticed many deficiencies recently in the packaging and labeling system and the laboratory control system. The packaging and labeling system deficiencies have involved insufficient procedures regarding line clearance and clean up." Director Graham specifically mentioned procedures to look for stuck labels on the line and to check rolls of labels for accurate count. The laboratory control system deficiencies have focused mainly on records and data handling. The agency has recently noticed a lack of analytical method validation, a lack of stability indicating methods, pages torn out of notebooks and the obliteration of raw data.

A copy of the compliance program guide can be obtained from the FDA web site at www.fda.gov/ora/cpgm. Look for document 7356.002.

Regulatory Issues / Requirements for Validation of Instruments Used for Laboratory Analysis

Presented by Erin Krohl, President of EH Krohl Counsulting, Inc.

Written by Lisa Eklund, Vice President

Erin Krohl, President of EH Krohl Consulting, Inc., gave an informative presentation at the PDA Southeast Chapter Spring Meeting. Her topic dealt with regulatory requirements for laboratory instruments. She discussed maintenance, calibration, regulatory and validation issues for laboratory equipment.

Ms. Krohl suggested the following items should be specified in the customer's equipment SOPs:

a) Service representatives should sign customer's equipment logs
b) Who performs calibration and maintenance (vendor or customer)
c) How often is this work performed
d) Does QA review vendor's work
e) Does customer issue declaration of acceptability of vendor's work
f) Is scheduled and nonscheduled maintenance handled the same way
g) How will vendor access computer network (i.e. guest user)
h) Recommended maintenance in instrument's manual should be followed
i) Storage capacity and back-up procedures
j) Evaluation of change controls
k) Specifications for system hardware and software

FDA auditors may review the following items in a "laboratory controls" based systems audit:
a) Appropriate design and capacity of equipment
b) Appropriate maintenance and operation of equipment
c) Location and environmental controls of equipment
d) SOPs and instrument manuals
e) Maintenance procedure, schedule, logs
f) Standardization / calibration procedure, schedule, logs
g) Standards used for calibration
h) 21 CFR Part 11 compliance
i) Validation / Qualification of equipment

Erin Krohl also presented an overview of equipment validation / qualification. She noted that a validation plan should be written first to define scope, responsibilities, procedures, acceptance criteria, results, etc. Below is a list of validation steps in the laboratory:

a) Design qualification (user requirements, functional specifications, operational specifications, and vendor qualification)
b) Installation qualification (correct software and hardware installation, does instrument work properly)
c) Operational qualification (does instrument perform your application properly)
d) Performance qualification (does instrument continue to work properly for your application, on-going performance tests)
e) Validation of spreadsheets and macros (include formulas, document expected and actual test results, compare manual calculations and computer calculations)
f) Vendor qualification should document whether they have a quality system, are they certified, is software validated by vendor, is validation documentation provided to customer)

After her presentation, Ms. Krohl also led a roundtable discussion about current laboratory issues. The hot topic was computer validation. Most of the discussion focused on specific requirements of 21 CFR Part 11. This regulation pertains to clinical and commercial products. Companies that use contract laboratories for clinical testing are responsible for ensuring the third party is complaint. Email may need to be included in the computer validation process. In addition to Part 58 for GLPs, FDA has a guidance document specifically for computer systems used in clinical trials.

On behalf on the PDA Southeast Chapter, I would like to thank Ms. Erin Krohl for her time and for her excellent presentation.

The PDA Southeast Chapter is Updating The Mailing List. Please email your updated information to Proflink@aol.com. Please include your email address. Thank you!

Second Annual PDA Southeast Chapter Golf Social

Friday, June 14, 2002 1:00pm Shot-gun Start

Hedingham Golf Club, Raleigh, NC

For Golf Sponsorship Information
contact:Susan_Moore@millipore.com

Captain's Choice Format
Individual Entrees only (team pairings will be random)
Teams are not Handicapped – for fun and networking
Team Prizes

Hole Prizes (longest drive, closest to the pin, etc)
Door Prizes
Complimentary Roving Beverage Cart
Catered Bar-B-Que Dinner

Entry Fee: Each entrant gets all this for **only $25**

No email registrations, please; entry fee must accompany registration. Make checks payable to 'PDA Southeast Chapter.' Questions? Email Terri: tmp12826@gsk.com

Registration Form

Name _____

Email Address _____

Company _____

Address _____

City _____ State _____ Zip _____

Daytime Phone _____

Approximate Score for 18 holes _____

Complete and return the registration form with $25 entry fee before May 31, 2002 to:

Terri Polson, GlaxoSmithKline, 5 Moore Dr., RTP, NC 27709

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- A continuous valve could be designed to remove all contents through the actuator. This author has no experience in implementing this idea and the opinion is that it is not a good option.
- The most feasible method is punching a hole in the bottom of the can to expel the contents into a sterile container.

Special devices have to be designed to perform any of the three methods. After the sample is further prepared with liquid media, the sample preparation may be heated to evaporate the propellant. Residual propellant in the sample preparation can cause microorganism inhibition.

Release Specifications

When compared to other non-sterile products, the inhalation specifications are lower microbial counts. The trend since the 1990s has been to move from 100 colony forming units (CFU) per gram or mL to lower numbers. For the total aerobic microbial count, the U.S. Pharmacopoeial Forums since 1996 have presented specifications of 100 CFU and greater for all products except "Inhalations."[4,5] For inhalation products, the total aerobic count is ≤ 10 CFU with an exception of non-pressurized powders where a limit of 100 CFU is given. In the European Pharmacopoeia, a specification of "not more than" 100 CFU is presented for the total aerobic and fungi combined count. A recent proposal for international harmonization was 50 CFU for the total count. The downward trend was triggered, in part, from cases of contaminated inhalant products possibly infecting patients. The contaminants were gram negative rod organisms that are commonly found in water, which is not typically in MDI and DPI formulations.[6,7,8] The publicized contamination problems have primarily been from aqueous inhalers, which are now required to be manufactured as steriles. [9]

Summary

Inhalation products pose unique challenges with regards to microbiological quality. When performing release testing, DPIs and MDIs have steps that are not encountered for other non-sterile products so require creativity on the part of the analyst. They have inherent antimicrobial properties, particularly the MDIs, so have low numbers of microorganisms in them. The expectation of regulatory agencies, particularly the United States, has been low numerical microbial specifications.

There are ample challenges with inhalation products!

References:

1 Sawyer, E., et. al., "Microorganism Survival in Non-CFC Propellant P134a and a Combination of CFC Propellants P11 and P12," *Pharmaceutical Technology*, March 2001, pp. 90-96.

2 M. Dower, Ed., "Pharmaceutical Basics, Inc. (PBI) Recalls Generic Metaproterenol," *Scrip World Pharmaceutical News* 1729(6), 1992.

3 M. Dower, Ed., "Copley on Albuterol Contaminant," *Scrip World Pharmaceutical News* 1913(4), 1994.

4 U.S. Pharmacopeial Forum 22(6), Nov.-Dec. 1996, p. 3102.

5 U.S. Pharmacopeial Forum 25(2), Mar.-Apr. 1999, p. 7789

6 M. Dower, Ed., "Pharmaceutical Basics, Inc. (PBI) Recalls Generic Metaproterenol," *Scrip World Pharmaceutical News* 1729(6), 1992.

7 M. Dower, Ed., "Copley on Albuterol Contaminant," *Scrip World Pharmaceutical News* 1913(4), 1994.

8 M. Dower, Ed., "Copley Fights Back," *Scrip World Pharmaceutical News* 2008(15), Mar 1995

9 "Guidance for Industry, Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation-Small Entity Compliance Guide," U.S. Food and Drug Administration, Small Entity Compliance Guides, November 2001.

Mark your Calendars for the following PDA Southeast Chapter Upcoming Events!

Friday, June 14, 2002
PDA Southeast Chapter Golf Social, Hedingham Golf Club

Thursday, October 24, 2002
PDA Southeast Chapter, Fall Meeting and Vendor Show
Sheraton Imperial, RTP

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108 Large Oaks Drive
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