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In This Issue

FUTURE TOPICS:

Monitoring Issues during Aseptic Filling Operations (both viable and non-viable particles) Myron Dittmer

Three Part Series on New OOS Guidance Mina Gerber

Basic Elements of Statistical Process Control
Stanley N. Deming

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HVAC Validation – Points to Consider

By Myron F. Dittmer, Jr., MFD & Associates
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The saying, *"Chance favors the prepared Mind"*, also applies when validating HVAC systems. The chance of success increases substantially when a strong effort is put into the planning phase. HVAC validation projects are complex, involve multiple and diverse components and subsystems, diverse trades and specialties, and in include complex automation control and monitoring systems.

An HVAC system is the key utility system that directly impacts the ability of clean rooms to provide the necessary environmental parameters to successfully run biotech or pharmaceutical processes. These environmental parameters include temperature, humidity, room differential pressure, air flow, non-viable and viable particulates, and room air change rates. An issue with any number of these parameters can create significant problems for manufacturing processes particularly for critical downstream operations (e.g., aseptic filling), that require high cleanliness levels and maintenance of critical and cascading pressurization zones.

In the following discussion, I will provide some points to consider that will help a company execute a successful HVAC validation project. Space limitations prevent me from going into greater depth but hopefully the information provided below will be of benefit to you in future HVAC projects.

Note: For the purposes of this discussion, it is assumed that the HVAC system has been properly designed to meet process and regulatory agency requirements (to meet US or overseas regulatory requirements

An HVAC validation project may be divided into three fundamental phases: (1) planning/management phase, (2) protocol development phase, and (3) project execution/approval phase.

The ***planning/management*** phase is the most important phase of the project since it sets the tone and provides guidelines and objectives for the project. If this phase is not performed or not planned properly, the project will degrade rapidly from this point forward. This author strongly suggests developing a Validation Master Plan (VMP), to define the elements, goals, and objectives of the project. This can be a simple document that that describes the overall project, the Who, What, Where, and When, and it should be signed-off by all groups participating in the project, including Manufacturing, Quality Assurance/Quality Control, Facility, Engineering, and Regulatory. Having everyone buy into the project, guarantees that all groups will provide the support needed for the project. The VMP will be the ***"road map"*** for everyone to follow as the project moves forward into the other phases and it will provide everyone involved with the same information. The VMP should be flexible enough so that it can be periodically updated when significant changes are made to the original VMP. These changes can be added to the original VMP as addenda. The VMP breaks down the project into its major elements which typically include:

- **Introduction:** includes the overview of the project along with purpose and Environmental Plan (acceptance criteria for all testing to be performed)
- **Reference Documents:** SOPs needed to execute the project, commissioning reports, balancing reports, submittals for equipment/system, system drawings, operation/maintenance manuals, etc.
- **HVAC Design Description:** how it works, clean rooms included for individual air handlers that make up the system, humidifiers, heating/cooling coils, supply/exhaust fans, HEPA filters, dampers, monitoring and controls, utility feeds (electrical, steam, air, glycol, gas), etc.
- **Project Organization:** how the project will be run, monitored, and changes implemented and deviation addressed. Also, include contributions by support groups such as Engineering, Facilities, QA, and QC.
- **Re-Validation Activities:** discussion of pre-validation
- **Validation Protocols:** describe the types of validation protocols to be developed and executed (e.g., Installation, Operation, and Performance Qualification protocols)
- **Schedule:** list a proposed schedule for execution (usually in the form of a project timeline)

To ensure that all elements of the VMP are executed when required and to monitor progress, a Project Leader should be designated. This person is usually a validation engineer but it can also be another knowledgeable and experienced person. The person selected must be skilled in multi-tasking, troubleshooting, problem solving, decision making, and generating team spirit. The Project Leader shall report back to the Validation Committee whose representatives come from Quality Assurance, Quality Control, Manufacturing, Regulatory, Facility, and Engineering. The Committee shall meet regularly to assist the Project Leader in monitoring progress, to authorize re-allocation of resources when required, and to provide input and consensus when critical decisions or actions are required.

The ***protocol development phase*** involves the development, review and pre-approval of HVAC validation protocols. The review and approval process typically involves Validation, Engineering,

Please see remainder of article on page 7.

NEW ENGLAND PDA NEWSLETTER

09 Nov 07 Volume 2, Number 3 Page 3 of 8

Connecting People, Science and Regulation

A Brief Introduction to Extractables & Leachables: Or, Is There Something *Extra* in My Drug Product?

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A major issue of concern in the formulation of an active pharmaceutical ingredient is its stability, both short and long term. As is appropriate, the early focus is almost exclusively on the active pharmaceutical ingredient (API): concentration, purity, and related substances that may be generated upon storage. A stability-indicating HPLC method is developed specifically to reveal degradation products of the API upon storage. However, as the API and its formulation are optimized, so should the storage conditions, which include the container-closure system. According to the FDA, the container-closure system should guarantee the protection, compatibility, safety, and performance of the drug product[1]. Primary packaging components refer to those that at any time will have direct contact with the dosage form[1]. Often, drug product is removed from its primary packaging and prepared for injection or infusion in plastic containers; the transfer to a secondary container brings about additional safety and performance issues.

Leachables are compounds that migrate into the formulation from the elastomeric or plastic components, or coatings of the container and closure system as a result of direct contact with the formulation. Extractables are components that can be extracted from elastomeric or plastic components, or coatings of the container closure system when in contact with appropriate solvent(s)[2]. At the appropriate time in the development of the formulation, both extractables and leachables testing should be executed. Extractables testing will evaluate the introduction of chemicals into a solution under aggressive conditions, which may vary temperature, solvent, or duration. Extractables may represent a potential worst case scenario. Leachables testing will also evaluate the introduction of chemicals into a solution, but study conditions are selected that mimic those intended for normal storage of the product and are monitored during the product's shelf life.

A typical initial container choice is a clear Type 1 glass vial. Although Type 1 glass does not eliminate the need for extractables testing, the use of plastic containers requires a more thorough investigation as plasticizers, stabilizers, monomers, lubricants, or antioxidants may be incorporated into its manufacturing. However, plastic packaging offers significant advantages over glass, such as cost, contribution to overall product weight, and impact resistance; the potential overall value of plastic packaging may well be worth the cost of extractable testing. Extractables may not arise exclusively from the container-closure configuration, but during drug product manufacturing. Careful and systematic extractables characterization reveals the identity, quantity, and source. In contrast to extractables, a leachable chemical may migrate into the drug product upon storage. Leachables may be extractables or not, but a thorough characterization of extractables likely provides the best foundation for long-term leachable studies.

Containers for parenteral medications should not interact with the formulation, either physically or chemically. An example of physical interaction is the adsorption of the API to container walls. In this situation, administrable API concentration is reduced but purity is not likely to be affected by such a mechanism.

However, a chemical interaction may induce degradation or leach chemicals from the container into a solution. Typically, chemicals that are leached from the container are not detected in methods used to characterize the fill solution itself. Leached chemicals may go undetected unless specific tests are executed to determine their presence. Because of the sensitivity and specificity of mass spectrometry (MS), coupling MS to liquid or gas chromatographic (LC or GC) methods provides a definitive and effective tool for identifying unknown impurities and degradation products[3], as well as leachables and extractables. It is an oversimplification when desirable drug recovery and purity data are used as the exclusive indicator of compatibility between the formulation and the container.

Because of sensitivity in certain groups (neonates, pregnant women, dialysis patients) di-ethylhexyl-phthalate (DEHP), a plasticizer used to make polyvinyl chloride and present in PVC-based products, is of particular concern. As DEHP is not chemically linked to PVC, it may be a likely leachable. Although PVC is not a common plastic for drug product storage, it commonly encountered in IV-based solutions and infusion tubing sets. A caution in the analysis of leachable chemicals however is that MS instrumentation may be plumbed with plastic tubing that can contribute background levels of DEHP. An additional caution is that acetonitrile, commonly used as a mobile phase component, can extract DEHP. Therefore, it is important to have background levels of DEHP characterized to ensure that detected amounts are not improperly assigned to the drug product or its interaction with administration equipment.

The storage and delivery systems selected for a drug product should guarantee safe, reproducible, assured delivery of the intended drug product, without anything "extra" introduced.

References

1. FDA Guidance on Container Closure Systems for Packaging Human Drugs and Biologics, U.S. Department of Health and Human Services, FDA, May 1999. http://www.fda.gov/cber/gdlns/cntanr.pdf
2. ITFG/IPAC TECHNICAL TEAM: CMC Leachables and Extractables; www.fda.gov/ohrms/dockets/ac/00/slides/3609s1o.ppt
3. D. Albert, Evaluating Pharmaceutical Container Closure Systems; Pharmaceutical & Medical Packaging News, March 2004.

PRESIDENT'S MESSAGE : **NEPDA 2007 Recap and Beyond** ***By Louis Zaczkiewicz, NEPDA President***

This has been a great year for the NEPDA and the PDA with increased involvement by members and sponsors during our focus on the PDA's Technical Reports: Chromatography Validation (TR14), Cold Chain Management (TR39), Sterilizing Filtration (TR26 & TR40), Project Portfolio Management and Steam Sterilization (TR1). Our speakers included Stephen M. Notarnicola, PhD; Susan J. Schniepp; Sarvang Mishra; Henry Ames; Jerold Martin; Leesa McBurnie; Dan Stavola; Donald J. Drew and Michael Finger. We had facility tours of Charles River Laboratories, Sypris Test and Measurement Laboratory and Millipore. Our meetings have been sponsored by Masy Systems, The Chisholm/Pall Corporation, CSSC, Blue Stream Laboratories, Associates of Cape Cod, Sensitech, World Courier, High Purity New England/Meissner, Millipore, Sartorius, Hyaluron Contract Manufacturing, Rapid Micro Biosystems, Getinge Inc., Process Control Solutions, Commissioning Agents Inc., GE Industrial Sensing and SGS – Life Science Services. Because of the gracious support of these sponsors, we've been able to add free appetizers and a complimentary drink for 3 of our dinner-meetings.

We have a great planning committee: Jerry Boudreau, President-Elect; Rusty Morrison, Treasurer; Melissa Smith, Secretary; Myron Dittmer, Member-at-Large, Bruce Rotker, Member-at-Large, Maryellen Brown, Mark Staples, Kim Rauenzahn, Göran Bringert, Mark Sitcoske, Sarvang Mishra, Michael Fried, Shawn Kinney, Peter Harris, James Butler, Jim Morris and Monique Sprueill. We are especially thankful to Hyaluron Contract

Manufacturing for hosting all of our business meetings.

We published 4 chapter newsletters and introduced a sponsorship program for them. We've introduced greatly reduced pricing for active college students and unemployed or retired PDA members. We have introduced credit card registrations and remodeled our chapter website with the awesome work of the PDA global office staff of Ta-Mela Jeffries, Hassana Howe, Nahid Kiani and volunteer Henry Kwan.

The PDA is introducing many new and revised technical reports that members automatically receive. They are also increasing membership value by providing members with a new benefit: the "International Pharmaceutical Quality" journal. This is in addition to the enhanced web features of the PDA Connector online, PDA Letter in print and online, discussion and technical support group opportunities, education courses both at TRI and online, student programs and PDA conferences (Annual, FDA and Pre-filled Syringe).

So how do we top that? Look forward to meetings on Process Validation on January 9, Aseptic Fill Simulation with a tour of the Massachusetts Biologics Laboratory on March 12, Environmental Monitoring and Validation of Isolators along with a tour of the Baker Company on May 16 [special Friday meeting so that you could consider staying up in Maine for an extra day or so], and meetings on September 10 and November 12 with topics to be determined. At our September event, we will be having our chapter elections.

We are putting together some new programs for which we could use help. We are planning on helping at the Massachusetts Science Fair and present monetary awards to the science projects that best fit with the PDA focus. We hope to have the winner present at one of our subsequent dinner meetings. We also are developing a relationship with the Middlesex Community College to help their students become involved in the PDA. Here we could use some help with employment opportunities for the students who complete their biotechnology program.
As always, if you want to help with the programs listed or have some great ideas for new ones, feel free to contact one of the planning committee members or myself.

Want to write an article ?
Email Melissa@MJQualityysolutions.com

Connecting People, Science and Regulation

The New England Chapter of the PDA is pleased to announce the ***availability of advertising opportunities in our newly launched newsletter.*** Since its inception in 1988, our chapter has seen a significant growth in membership and participation. Our newsletter has the following reach:

- Our direct e-mail distribution reaches over 1,200 contacts throughout New England.
- Our membership includes people from manufacturing, research, QA, QC, engineering, contract manufacturers, consultants, regulatory, ***etc.***
- The newsletter is promoted at New England PDA's bi-monthly dinner meetings, often with company tours, which regularly attract 50-100 attendees.
- The newsletter is posted to our chapter's website at Global PDA (www.pda.org), an organization that has over 10,000 members.

We offer vendors, consultants, operating companies and other organizations the opportunity to promote themselves and also support the NE PDA Chapter by purchasing advertising in our newsletters

Upcoming Publication Schedule:

Issues	Cost	Deadline
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Thank you from the New England PDA!
Louis Zaczkiewicz, ***President***

HVAC Validation – Points to Consider

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Quality Assurance, and Regulatory groups (other groups may be added if applicable such as Quality Control, Facilities, etc.). The VMP should provide everyone with a general schedule for these activities and this schedule will need to be updated as events unfold due to unanticipated delays, equipment failures, retesting, etc. Failure to update this schedule periodically will most certainly cause delays and coordination issues with other ongoing activities.

Validation protocols developed include, (1) ***Installation Qualification (IQ)***, (2) ***Operation Qualification (OQ)***, and (3) ***Performance Qualification (PQ).*** Briefly described, the IQ confirms that the system (and component parts) has been properly installed to meet design requirements, the OQ confirms that the system (and component parts) operates according to design and company requirements, and the PQ confirms that system performance has been challenged and meets final operational requirements. The PQ protocol usually involves monitoring important environmental parameters over a specified time period. These parameters include temperature, humidity, viable and non-viable particulates, and room pressurization and evaluating these parameters during periods of **"at rest"** (no staff activity and with equipment running) and **"in operation"** (staff activity and with equipment running).

Many companies are now streamlining their HVAC IQ and OQ protocols by defining the limits of this validation to only downstream system components and areas. For instance, these companies have defined the limit of validation for the system from downstream room re-heat devices to the clean room. This can significantly reduce the time and labor required to complete IQ and OQ activities. However, this can only be accomplished by having a well documented commissioning program that includes confirmation of installation and operation testing for all the upstream components not included in the IQ and OQ validation protocols.

A biotech company in the Boston area used this approach for their HVAC systems in the construction and validation of their new 155,000 sq. ft. bulk and final product manufacturing facility. The acceptability of this approach is demonstrated by their recent successful FDA Pre-Approval Inspection (PAI).

The ***protocol execution phase*** is the last phase of the project and involves the compilation of all information, test results, and associated documentation, and a summary of all acceptance criteria met summarized in a final report. All deviations encountered during the execution of each protocol must be completely resolved. The final report is then circulated to protocol signatories for their review and approval.

The process flow diagram on page 8 provides a summary of the many different activities involved during protocol development and execution phases of the project and the interrelationships.

Process Flow Diagram from M. Dittmer Article, page 7.