PDA Southeast Chapter

SOUTHEAST CHAPTER
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Letter From the President

June, 2003

A very successful Southeast Chapter Spring Meeting was held on April 17, 2003 in Research Triangle Park. Member participation was good and the presentations were relevant and interesting. Round table discussions on Validation , Environmental Monitoring, and Compliance issues were well attended. Thanks to Biotest Diagnostics Corp, Associates of Cape Cod, Inc., Commissioning Agents, Inc., Lloyd's Register Serentec, Pharma-Sys, Inc., CRB Consulting Engineers, Inc., Millipore Corp., and Phil Ellis Associates, Inc. for sponsoring the event.

Look for event information on the PDA Southeast Chapter website at pdase.org.

Our upcoming events include a Golf Social on June 6, 2003 and a Fall Meeting September 23, 2003. We hope to see everyone there. Look for event information on the PDA Southeast Chapter website at pdase.org.

The chapter charter requires that elections be held every two years; therefore, we will be holding elections this fall. Elected offices include the President, Vice President, Treasurer, and Secretary. You must be a PDA National member to serve as a Chapter Officer. I would like to encourage anyone who is interested in serving as an officer to contact me or the other Chapter Officers as soon as possible.

We will also need a Nominating Committee. The Nominating Committee will be responsible for providing a slate of candidates for each office to the Executive Committee. You do not have to be a National PDA member to work on this committee. The Nominating Committee is a short term commitment so if you have thought about participating but don't have much time, this is a great opportunity for you to get involved. I hope to hear from you.

Mary

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Fundamentals of FDA's Systems Based Inspection Approach

Presented by Robert L. Lewis, President, IHL Consulting Group
Written by Kim Speight, Quality Associate III, Quality Compliance for DSM Pharmaceuticals, Inc

The evolution of the quality systems inspection techniques

(QSIT), which began in the Medical Device Industry, has now become the new approach for good manufacturing practices (GMP) inspections performed by the FDA. Several factors were taken into consideration for implementing QSIT, including the fact that the average drug firm was only being inspected every 7 years, instead of the statutory requirement of every two years. The agency was having trouble meeting its schedule and too much time was being spent on certain inspections.

What should industry expect with the new approach? According to speaker, Robert L. Lewis, President, IHL Consulting Group, the approach is not a drastic change to what the FDA has performed in the past. However, the approach will review a drug company's quality systems for a "profile class" as opposed to a single drug. This method can have a drastic impact on the company, in that if one system is deemed "out of control", then all profile classes are deemed unacceptable. On the other hand, the method may eventually mean fewer inspections if the agency becomes confident in a company's quality systems.

The FDA investigator has three inspectional options to utilize in a GMP inspection. The full inspection option reviews the quality system plus three additional systems. This option is typically used for a new facility, a company with a poor compliance history, or if a company is adding a new profile class. The abbreviated inspection option includes the quality system plus 1 other system, which is typically performed at sites with good compliance history or during a routine surveillance. Lastly, the compliance inspection (equivalent to the full inspection option) is performed for follow up to regulatory actions, for cause inspections, and for companies with many defect reports, such as recalls and complaints. While the FDA will never be able to look at every system in an inspection, there are six main systems from which they choose. The six systems are:

The **Quality System** will always be one of the systems that the FDA reviews. Within the quality system, the FDA is looking to see how a company responds to problems and if all problems are captured and addressed. Corrective actions within the quality system must be effective and performed in a timely manner. In addition, the investigator's are taught that a good judge of the attitude of management, Quality's influence and leadership in the company, and the company's commitment to compliance reveals the way it handles true problems in their facility.

The **Facilities and Equipment System** includes cleaning and cleaning validation; HVAC/ environmental controls, containment (potential for cross contamination); changes in critical areas; WFI/purified water system; equipment maintenance and calibration; and equipment qualification (including computer validation and security).

The **Materials System** includes control of incoming materials and components (quarantine, storage,

continued from page 2 (Fundamentals)

release and use); validation of computerized inventory control processes, drug storage, distribution controls and records; release procedures (who has authority, at risk, etc.); retest procedures; and changes in materials.

The **Production System** includes batch record review; component preparation (depyrogenation, sterilization of container/ closures, etc.); hold-times, in-process controls, use logs, etc.; identification/ documentation of critical process parameters; contemporaneous and complete batch production documentation; and process validation.

The **Packaging and Labeling System** includes controls of master copies; issuance and restriction; changes in labeling; line clearance options; reconciliation procedures (if applicable); and vision system validation.

The **Laboratory Control System** includes adequacy of equipment for intended use; calibration and maintenance; security of computer systems; change control; procedures, testing, analytical methodology, development and verification/ validation; lab documentation ; and adherence to out of specification procedures.

As Robert L. Lewis mentioned, in review of the systems listed above, there are also several intangible factors that can be revealed. These factors are corporate culture, FDA's perception of the company, company decision making, management oversight, attitude, patterns of behavior/patterns of failure, and ultimately the company's state of control.

"A system is out of control if the quality, identity, strength and purity of the products resulting from that system(s) cannot be assured adequately. Documented cGMP deficiencies provided the evidence for concluding that a system is not operating in a state of control."

Environmental Monitoring Round Table

Written by Lucia Clontz, Director of QC Microbiology/Environmental Services and QC Raw Materials, Diosynth-RTP and Jessica Sasser, DSM

Facilitators: Carol Walker Rusty Fulghum
Kip Lopez

Environmental monitoring (EM) continues to be one of the hot topics of discussion in the pharmaceutical and biotechnology industry. The fact that the regulatory agencies routinely include review of EM programs and trended data during inspections only adds to the attention given by companies to this area of the business. The field of monitoring controlled environments is also changing at a fast pace. New pieces of equipment are being introduced to the market and new ideas on how one should manage an EM program have also been brought to light.

During the round table discussions that took place at the PDA Southeast Chapter meeting on April 17, 2003, many of the hot topics involving EM were discussed. Below you will find a summary of the two Q&A sessions that were moderated by our colleagues in the industry.

Q. How does FDA view EM in non-sterile manufacturing in relation to product release?

A1. Never link to batch release.
- Do Investigate
- Do link to what is going on in the room
- Non-sterile process flows to sterile process. Do not worry about EM until sterile process starts.

There is an investigator in this area that expects to see product impact statement when an excursion occurs.

A2 De-link where applicable. Must have a robust EM program and in-process controls, such as sterile filtration. Created a Master Plan to address the EM program and data evaluation as related to batch release.

A3 For sterile manufacturing, all excursions, even the ones nowhere near the fill are still considered. Investigations are completed prior to product release.

A4 Created Master Plan to rationalize the connection between EM and batch release for certain steps of the process or types of processes. For example, during fermentation we do not link EM to batch release since we are dealing with organisms anyway.

continued on page 4

continued from page 3 (Environmental Monitoring)

A5 We do not address out-of-trend or out-of-action excursion for non-viable particulates as far as batch release is concerned. This is more of a room classification issue anyway.

Q. How do you set up your Alert and Action Levels?

A1 Our company harmonizes the recommendations from EU and FDA and uses the most stringent criterion; for non-sterile manufacturing, we use rationales for why the levels are less stringent than the industry recommended ones. The alert and action levels must make sense, be logical, demonstrate process flow, and people flow.

A2 Our company usually uses the most stringent guideline across the board.

Q. Where is the rationale for establishing alert and action levels captured?

A. In a governing EM SOP or Master Plan.

Q. Non-viable particulate monitoring discussion:

A1. MCA cited our company for not cleaning the interior of a non-viable particle counter unit. Now, we must figure out how to clean the inside of the equipment to avoid cross-contamination.

A2. Our company is in the process of acquiring Met-One units with HEPA filters. Although the intake air is filtered, the inspector was concerned with the air exhausted from the unit.

Q. If an excursion occurs during continuous monitoring, what do you do?

A. Document and investigate.

Q. Do you evaluate non-viable results based on each value or on an average of the replicate results?

A1. Do not average.

A2. Do not average in Class 100, only in Class 1,000 or Class 10,000.

Comment: ISO Documents do not address routine monitoring for non-viable particulates only classification verification.

Q. How to handle mold isolates: What does the FDA say about molds?

A1. Unless you have a type of screening process, FDA expects firms to control the environment for absence of mold, spore-forming organisms, and gram-negative organisms.

A2. Depending on the firm's compliance rating with the agency, firm may get away with not screening for specific organisms.

A3. Our company discussed this issue with an FDA investigator who pointed out alert and action levels are based on counts only, unless a firm has identified objectionable organism(s) to be screened, based on product quality and safety of target patient population.

Q. Do you do specific fungal and/or anaerobic monitoring?

A1. We perform routine EM using dual incubation (same medium incubated at both temperature ranges of 30-35°C and 20-25°C) for recovery of both bacteria and fungi.

A2. A company should perform EM using specific fungal medium alongside all-purpose medium (TSA) for a period of time. Then, most likely you will have proof (qualification) that you can reduce or eliminate use of special fungal medium.

A3. Perform EM using specific anaerobic medium/incubation once a quarter because we use *Clostridium* BIs and we want to make sure they are not contaminating the environment.

Q. Qualification of EM equipment. Is it necessary? How do you go about qualifying EM equipment?

A1. Validation of environmental monitoring equipment/method is required. One method is to inoculate plate, run sample, and test to make sure you are not desiccating the media. Also, must make sure you are pulling in the amount of air you are claiming the equipment pulls in and the timer is calibrated.

A2. Side-by-side study using two or more instruments/media is very important. Perform study up-front or whenever changing instruments/methods.

Comment: Our company has a requirement of 70% recovery as compared to existing unit/method. However, using 0.3-0.5 log variability as a measure of no difference in methodologies is also acceptable.

A3. If a company changes methods/equipment, must re-evaluate alert levels which are based on historical data.

Comment: When changing from one method to another, it is difficult to run side-by-side and to see the correlation. Do not expect alert levels to hold true and trends to stay the same.

A4. Europe has always required settling plates and until recently, with a four-hour exposure time. Must qualify settling plate exposure times.

continued on page 5

continued from page 4 (Environmental Monitoring)

Q. Why should individual customers have to validate the instruments when the instruments are calibrated?
A. Not every company runs their temperature and humidity at the same levels.

Q. What type of program do you have for trending EM data?
A1. Once a quarter
A2. Once a month. Management must be involved.

Q. How do you choose what to trend? Do you trend zeros?
A1. Yes, we trend zeros. We perform month-to-month comparisons.
A2. Percent normalization of data is much better. Graphs are better than tables.

Q. How do you handle TNTC in a trend?
A. We establish 300 or another number to reflect TNTC.

Q. Are you re-evaluating Alert and Action Levels on a periodic basis?
A1. We perform annual re-calculation using 95% for Alert and 99% for action.
A2. The expectation is that the alert level should go down. Must evaluate data for adverse trends.
A3. Alert levels are set at 80% of previous already established level.
A4. USP says you must have alert levels and re-evaluate Alert and Action levels periodically. They must be meaningful to reflect how your area is running – must run statistics periodically to set appropriate levels using daily actual numbers.

Suggestion: Perform a search on Alert and Action levels on the PDA web site.

Q. Do you trend data by room or classified area?
A1. Trend by classified area.
A2. Trend by room.

Q. What do you do when you exceed an alert or action level?
A1. Alert level is a red flag only. Three alerts constitute one action. For both alert and action, area manager is notified.
A2. Multiple alerts in the same area, and consecutive alerts for the same site constitute action. Must look at possible variability in position of instrument within the room.

Q. How many people ID Alert and/or Action Level isolates?
A1. Aseptic Fill area: ID all alert and action level isolates.
A2. Gram stain alert isolates and perform full ID for action isolates

Q. How many people are using an EM software?
A1. Use LIMS. Difficult to trend. Export data to another program. Validated the exporting of data to the other system.
A2. Use EMSS. System does site-to-site trends very well but does not export data very well. EMSS can be customized. Not so good for overall trending but new upgrade will have customized reports.
A3. In process of evaluating the software from Novatek.

Q. What is the classification of your Weigh & Dispense area?
A. Class 100,000 plus hood for dust collection system.
Note: rest of the group agreed with this approach.

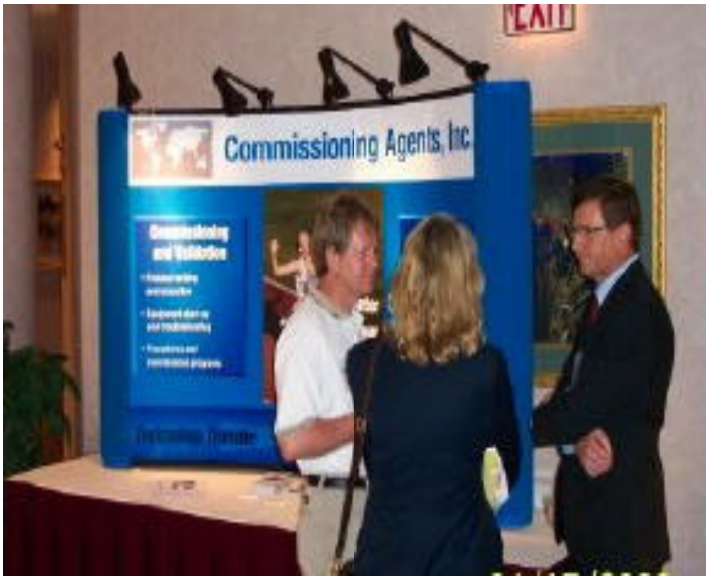
Q. How often do you use sporicidal agents?
A1. Use 400 ppm of sodium hypochlorite as needed.
A2. Use Spor-Klenz weekly.

Comment: Corrosion problems with sporicidal agents

Q. Do you perform bioburden testing during cleaning validations?
A. Across industry cleaning validation is mostly from a chemical viewpoint.

Q. Was bioburden swabbing validated?
A. Did not call it cleaning validation. Called it evaluation. Modeled sampling plan after chemical plan. Evaluate micro versus TOC. After you pass this, you do not have to use swabs only rinses. Could not validate recovery above 25%.

Remember to contact Kip Lopez at lopezk1@wyeth.com to update your member contact information, especially your email address. The PDA Southeast Chapter Newsletter will be emailed to members and will be posted on the web site. In addition, visit www.pdase.org for information on all of the upcoming Chapter events!



Efficient Models for Validation Staffing and Document Development

Presented by Bruce Stevens, Validation Manager, Biogen, RTP
Written by Christine Cramer, Validation Specialist, O'Neal, Inc.

Bruce Stevens, Validation Manager of Biogen at RTP, presented "Efficient Models for Validation Staffing and Document Development" at the PDA Southeast Chapter Spring Meeting. Tired of circumventing pitfalls of validation programs that rely too heavily on consultants or are performed by the traditional large-in-house validation team, Bruce has posited a way to fundamentally improve rather than patch the system.

He describes an organizational structure that would best support an idealized process; a process which would deliver:

- Abbreviated staffing and time frames for complete validation
- Minimal documentation and consistent approach/procedures
- Technical accuracy and improved understanding of the test subject

Enumerating advantages and disadvantages of the three basic validation staffing models (VSM), he discussed what is ordinarily seen when using traditional approaches of: a dedicated validation group, a consultant-based staff or a project-based multidisciplinary team. Building on the recognizable strengths from each of these basic models, he draws a cohesive picture of a streamlined and efficient Hybrid Validation Staffing Model for staffing supported by clearly defined Modular Documentation Development guidelines to provide us with an optimized validation system.

Utilizing a minimal core team of validation professionals to manage projects and ensure procedural continuity, the Hybrid VSM allows flexibility to increase staff when work-loads are high and draw from all divisions of the company personnel. A project validation team will be led or directed by a company validation

professional and may call on any department associated with the system. System owners are involved and technical expertise may be brought in from what ever arena works; first looking in-house where available, or bringing in vendor staff or consultants where needed. Included in the project team, especially to execute testing, could be engineering, operational and maintenance staff. Using staff that will later operate or maintain the equipment to write protocols and/or perform validation testing assures that:

- Validation testing will reckon on the proposed uses of equipment or facilities
- Lessons learned during the validation will be functionally incorporated by users
- Validation is recognized as a necessary and useful precursor to online operation

Crucial to the success of this model is establishing fully delineated and agreed upon roles and responsibilities of all affected departments and individuals on the team, and establishing clear leadership and authority of the manager of each project.

A modular approach to document development looks to incorporate the best of the flexibility and specificity found with the oft used method of writing a protocol from scratch for each piece of equipment with the conformity and instant availability of the template method.

Certain test activities are common such as pressure/time, temperature mapping, or security testing. SOPs delineating test instructions are the technical specifications for how to perform a test and can be combined with specific test scripts as needed. These SOPs would include forms to be used for specifying test parameters and recording data. This method provides the benefit of templates without restricting creativity needed to customize validation activity. This can be a very efficient model which:

- encourages rapid document development
- requires fewer validation staff members
- provides consistency over time and across sites

The modular approach to document development is labor intensive at the beginning with the SOP writing and form development. It still requires traditional preapproval of all procedures/test plans and final acceptance after testing and report completion.

Thank you Bruce, for a clearly thought out and well presented concept. The talk was well received and obviously struck a responsive cord when measured by audience participation, anecdotal contributions and questioning.

Validation Round Table Sessions

Written by Christine Cramer, O'Neal, Inc.

Facilitators: Michael S. Korczynski, Senior Vice-President, MIKKOR Enterprises, Inc.
Tony Pavell, Validation Manager/Sterile Technologies, Cardinal Health
Bruce Stevens, Validation Manager, Biogen

The Validation Q&A Roundtable was an open forum, with questions fielded by the panel facilitators and audience participation encouraged for not only questions, but additional comments and advice. Given the informal nature of the discussion, I have tried to relate the flow of information, asserting no claim of verisimilitude for the advice proffered and in general not attempting to attribute a question or comment to its source.

Process and Equipment Validation issues

Q. How do you ensure validation document traceability?
A. Set the same specification expectations for all work, with a set pattern of:
Requirements → Design → Tests/Matrix → Pre-approval match-up.
The link to see that the entire test matrix is covered is up to the initiating department. This may not be an adequate link to assure complete coverage in all cases.

Q. What is an appropriate time interval for review/retest to maintain a validated state?
(There is no single answer. We did not even agree on the term to be used for the subsequent validation efforts that follow the initial, complete validation of equipment or process. Some called it revalidation, others preferred periodic validation; validation continuum, or even a "continuous validation" may be accurate for some projects. While there may be some distinctions in those terms, they are subtle and for the purposes of this article I am going to use revalidation for brevity.)
A. a. The type of equipment or process that has been validated is a primary consideration. All items, whether process or equipment validation projects, need to be periodically examined, but a blanket 'revalidate every two years' was roundly condemned. Both the periodic frequency and the nature of the review should be set by company SOP or policy. The indicators, frequency, and evaluation factors

continued on Page 9

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continued from Page 7 (Validation Round Table)

for revalidation should be justified, clearly stating what is the review time interval and the actions required.
A. b. Steam sterilizers and lyophilizers are generally on an annual review cycle, including retesting. However, even here it appears that most companies do not perform a complete set of validation tests annually; consensus appeared to be that testing a few of the limits or test cycles is sufficient, with a complete revalidation at maybe five year intervals.

Comment: PDA may develop a validation guidance, as concurrent validation was a topic that the industry favored during the PDA/USP sterile products meeting on Sanibel island (2001). Would it be worthwhile to make the guidance a modular approach to performing concurrent validation (which is consistent with PAT (process analytical technology) strategies and eliminate or extend periodic validations?
A. a. Periodic evaluations are necessary, but expectations for annual reviews feels excessive.
A. b. There should be an expectation of annual checks of recovery time & heat distribution of autoclaves, refrigerators, incubators.
A. c. Disagreement: A validation needs to justify use of the equipment, not perpetuate work. What do you gain by doing a full test of a refrigerator that you wouldn't get from your routine monitoring if you use the worst place (warmest) position, or if you check a few placement areas to make sure the worst place remains the worst place?
A. d. A lot depends on your preventive maintenance program. Changes may be seen with overall testing that would not show up in a set point testing.
A. e. You still have ongoing data in the form of test batches and process monitoring.
A. f. If one guy does it will it become the "current" expectation and everyone will be required to do it even if it isn't a real need from a risk assessment or scientific need?
A. g. FDA should release guidance on what should be included in submissions to permit the use of PAT and/or concurrent validation. Mike Korczynski has submitted a proposal to the PDA to develop modules that would define in process (on-line) measurements for use in concurrent validation or implementation of PAT. The PDA Scientific Advisory Board is currently considering this proposal.
A. h. Should breakdown the modules of equipment / process /facility; with subsets of the equipment including lab equipment, computers and manufacturing.
A. i. FDA is beginning to look at risk assessment.
A. j. Changes are ongoing and the guidelines are helpful for scientific rationale and need to be applied to specific cases in light of your SOPs and policies.

Q. Is there a consensus that processes are undergoing revalidation?
A. The question is rather, should you? If it is required, then yes - If you see change over time, then yes. What does it matter? Annex 15 does not say what must be monitored or how often.
Suggestion is made that we, the industry, needs to push back, look at the long term benefits, examine what rationale is used. Utilize trending audits, APR (Annual Product Review). Companies seem to favor longer review schedules, seeing as much as a five year review schedule rather than annual

Q. Can periodic review be document review? Using what, some combination of preventive maintenance, change control and calibration records?
Q. What are the triggers to require a revalidation?
Q. How does change control fit in? Do you revalidate if there are no changes?
A. a. All your validation activity should be tracked, and reviewed within set time frames. The periodic review time will vary based on criticality and potential for changes to the system; this should be related in your validation master plan.
A. b. Additional triggers for initiating an in-depth revalidation testing protocol may be based on:

- Type of equipment or process
- Audit or review findings
- Changes in basic understanding of the process or testing limitations
- Changes in methodology of the process, the laboratory method, or the validation assumptions

A. c. Concept basis: establish limits of validation and establish specification then a slightly tighter limit yet to trend for avoiding revalidation; use values for "alert", "release", "action" limits. These data would be collected during routine QC testing or calibration testing.
A. d. Relate an analysis of routine process data to system control; you need criteria to recognize the process is in control – prove it is control
A. e. Technical innovations using PAT may be a relationship that will limit "revalidation".
May be able to do away with specific/discrete validation and go to "continuous" validation.
A. f. If there is equipment change, or evolution of the process , then review is needed. If your company has made changes in the way it performs related validation testing then the prior validation activities may need review.
A. g. Annual Product Review (APR), periodic (scheduled) quality review of any process can be the basis of your

continued on Page 10

continued from Page 9 (Validation Round Table)

periodic validation review cycle. APR; batch failures, change control and trend data are common triggers to alert validation review.

Additional comments:

- your quality department may take over routine sampling
- we have a validation specialist who writes up the results
- we have annual OQ
- depyrogenation, autoclave, media fill tests annually
- occasionally a company may do a full-blown revalidation, but most have cut back to a critical few parameters to test
- for steam sterilizers, annual master load validation and on 5 years repeat total validation testing of all load configurations

Q. Does anyone do a cool zone sterilization cycle?
A. We have done monitoring during change/shut down.
Q. How about HEPA in the hotzone? And what about particulates? Is anyone operating with no HEPAs in the hot zone?
A. Yes, infeed and out feed is HEPA filtered, but the hot zone has none; this is a situation where the hot zone uses radiant heat.

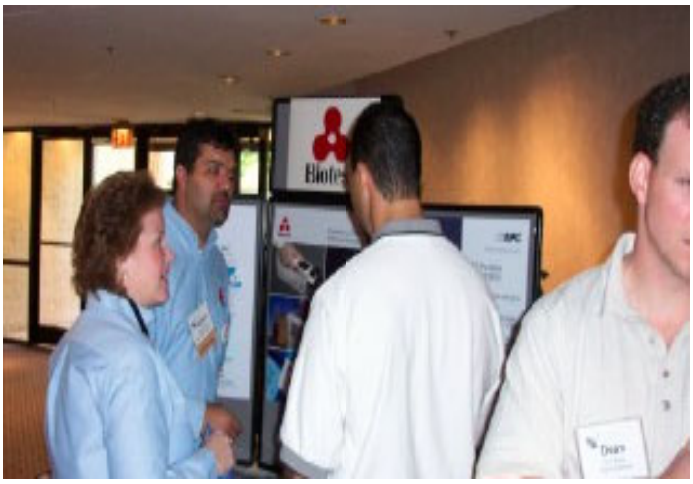
Q. Utilities – it has been suggested that we use a controlled inoculation to test the sanitization of our purified water system.
A. NO!
A. Don't do that!
A. It is an unjustified and unnecessary risk to introduce a contaminant. You could possibly use a self-contained biological ampoule for hot WFI that is heat sanitized. This would be a conservative test, since the capsule would have a lag time for the transition/penetration.
A. Would you want to put an ampoule in? Glass is fragile, when we use them in a tank we have them in a Teflon cage to protect them. Self-contained plastic modules might be considered.

Q. Does your OQ test factory limits as opposed to your company's worst case limits?
A. If engineering specification is tight it is sometimes used for the OQ parameters. More felt that the whole range of factory specifications for equipment should be in the OQ, so that IF usage were to change then a complete retest could be avoided. Qualifying the whole use of equipment; is more work up front, but easier for making later changes.

Parametric Release Testing
(writer's note: FDA provides EMEA (European Medicines Evaluation Agency) definition of Parametric Release as "a system of release that gives assurance that the product is of the intended quality based on the information collected during the manufacturing process and on the compliance with specific GMP requirements related to parametric release."

See also: http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-800.html)

Q. Parametric release, for steam (moist heat) vessels, what is it? Elaborate – Quality built in, statistical trending.
A. a. The values used for parametric release could be PAT and may obviate the need for periodic validation. Generally *Critical*, and *Secondary* process parameters are considered. Critical would include peak dwell time, average peak temperature, batch or lot release test results (not sterility testing results). Secondary criteria wouldn't necessarily be showstoppers, but might include backup glass thermometer data, min to max peak dwell temperature, autoclave or sterilizer chamber pressure, and parameters related to water as a sterilant. Generally F_0 is not considered a Critical parameter because F_0 can be achieved by variable time/temperature relationships. However one could define the target F_0 range expected from the defined time and temperature relationship



as a Secondary parameter CFR Part 211 requires a lab test to analyze a finished product. Parametric test may eliminate the sterility test but would still need some verification, i.e. a thermal indicator within the load. Include extended (for instance, two years) good performance data in the submission. So if one is using parametric release following approval, why would subsequent use of the continuous PAT data collection require revalidation; wouldn't it permit using the data without revalidation?
A. b. Parametric release, concurrent validation, PAT - use these for validation review.
A. c. Parametrics used incorrectly can be problematic. Write criteria carefully to avoid rejecting a batch where the deviation is not related to product quality.
A. d. You need some sort of automated system to gather continuous data for trending.
A. e. Parametric release is adequate when you have:

- Well documented and understand the process
- Predictable and measurable
- BI validated process
- Well supported rationale

continued on Page 11

continued from Page 10 (Validation Round Table)

You would still want an initial validation and years of support data, looking at pressure, chamber water level, etc.

Q. Would it be necessary to adapt a piece of equipment to collect this data? Would it be enough to put a monitor inside the load on a weekly basis to perform this check?
A. Establish what is the primary criteria on which you base your judgement that the product is sterile, and then on a run to run basis, each/every run would be tested on these primary criteria test point(s). There is then no value added in periodic validation if this routine testing is performed.

Q. Does parametric testing sound like it is relaxing criteria? Can we use information on a piece of equipment that is in general use?
A. Industry will work with the FDA (FDA has a senior person as a delegate on the PDA scientific advisory board). PAT will give some relief on product testing. Developing modules may help industry get started. It can save money on validation time and costs but limits would still remain stringent. We should consider certification limits, product specification limits including physical, chemical and microbiological limits that are set tighter than the certification values. Using parametric release (similar to PAT concept) and a monitor within the load (for a steam vessel) will give a better analysis than you would get from a validation test package.

Q. So you are proposing this as a logical step forward for the industry?
A. Industry has been collecting validation data since 1976. When is enough, enough? FDA is even beginning to relate to new procedures and risk assessment reasoning. Set up an outline or a module of how to measure a process, using HACCP, and get rid of periodic validations. Of course, prospective validation will always be needed.

Cleaning issues:

Q. Should we be targeting cleaning validation? Does validation ever stop?
A. a. May want to add addendum to validation as changes occur if new ideas are recognized.
Retrospective using data from historical batches is a valid concept to maintain a history of the process.
A. b. With analytical test on each lot, a cleaning monitoring program may target six months for a cleaning validation of a specific piece or type of equipment and rotate what is looked at each six months. Without equipment or process changes a complete revalidation may never be required.

Laboratory issues:

Q. What about revalidation of laboratory method or equipment? Can calibration be considered equivalent of an OQ?
A. a. Revalidation of laboratory equipment is new to many companies for either methods or equipment so there isn't much shared history to draw from.
A. b. After initial qualification , history may suffice to justify a longer interval between reviews. Use your secondary measurements as a trend monitor.
A. c. Lab equipment should be included in Master Validation Plan matrix. MVPs are the how/what/where plan and should include directives on how much validation, when/frequency and accept/reject criteria. Using flow diagrams including control points and risk assessment improves the process.

Q. Does a laboratory method validation need periodic testing?
A. a. Method verification using a critical test item or test point is all that should be required if there are no changes. Personnel changes are probably adequately tested with a supervised verification run, equivalent to a method transfer test protocol, using USP test definitions.
A. b. Refer also to USP <1225>, Validation of Compendial Methods; and the ICH-QA2 Guideline for Industry, Text on Validation of Analytical Procedures.

Compliance Round Table Session

Written by Lucia Clontz, Diosynth-RTP and Jessica Sasser, DSM

Facilitators: Stephanie Davenport,
Catalytica Pharmaceuticals (DSM)
Robert L. Lewis, IHL Consulting Group

Compliance issues are always of interest. We can remain familiar with the requirements by reading the regulations, but the practical applications vary over time and situations. Keeping the "current" in cGMP requires that we understand what the industry is doing and what technology changes are available and applied. Round table discussions offer excellent opportunities to exchange information on what's happening, why its happening and maybe opinions on what should be happening or what we can do about it.

Q. Media Fills – Why would vials used for volume checks that are destructive have to be incubated? They are not normally included with the "good" vials during a fill.
A. Intervention – Investigator wants to see it incubated. Must go through the motions of a normal fill. A comprehensive view of the process as a whole is needed.

Q. Cleaning Validation – Multiple products - Generics can be complex. How does the agency feel about bracketing and verification, not actual validation? What about selected checks of other products outside of most toxic compounds?
A. Acceptable to bracket with good rationale. Verification is crucial because humans vary by shift and person to person. Speaker views verification as enhanced.

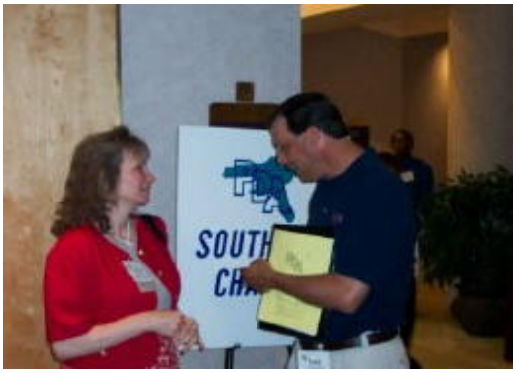
Q. How many systems-based inspections have Atlanta conducted in the last year?
A. Do not know. Most are pre-approval inspections with unique creative inspectors. Investigators do not always announce an inspection as system-based. They may call it a "GMP" or "routine" inspection.

Q. If an abbreviated inspection is being conducted, how long do the investigators stay?
A. Three days to a week is the normal length. In the NE, they are a lot lengthier. Atlanta inspectors want to get in and out.

Q. Non-forthcoming investigator – Said he was there due to a complaint received from a customer. Several hours passed before the company figured it out, and the investigator would not let them see the complaint.
A. New investigator

Q. What are the levels of controls for complaints in contract companies? How involved should we be? (API)
A. The contract company is fully responsible for the investigation. Not owning the product does not absolve the contract manufacturer. If the complaint applies to process at contract facility, you are fully responsible. Complaint must be transferred from the owner to the contractor. (Even if contract co. name is not included on the finished product label.)

Q. What is the liability standpoint if contractor does not know about the complaint?
A. Investigator will write up contractor and owner. There must be a mechanism for transferring the complaints.



Q. Does label have to include same requirements as finished product?
A. Yes

Q. What are the responsibilities of the contract manufacturer with Annual Product Review (APR) ?
A. Agency must look at site and how product is manufactured. Contractor must perform APR in depth. Contractor is at the mercy of the owner (applicant). Customer can make changes, contractor cannot. Contractor can make recommendations and document them and the communications with the customer. Contractors must protect themselves.

Q. Profile of classes and databases – How do we get info from FOI?
A. File a freedom of information (FOI) request form for information that is not public. Go to: http://www.fda.gov/foi/foia2.htm .

Q. Line clearances keep coming up – production vs. QA performing them – Customers want QA, but history shows production does good job.
A. FDA does not have a preference. It would be good if QA over saw the work. Just because QA is ultimately responsible, but that does not mean they have to be there when the operation is performed particularly where your historical data shows production is doing a good job.

continued on Page 13

continued from Page 12 (Compliance Round Table)

However, where there has been a product mix situation then I would expect QA presence during line clearance.

Q. Contract Manufacturer cited for decisions made by client – What is FDA's perception?
A. In order to get someone's attention, FDA will put it in writing to bring to a head! 483 keeps product from leaving the site. As contract manufacturers, we have to draw the line for minimal GMP expectations of what we must do. We have to be in control while running processes. Customer and contractor have to work together. Opinion: FDA must push on customers (applicants); one way is to call them while at the contractor plant.

Q. Lack of knowledge of the FDA Inspector is embarrassing – inappropriate waving at aseptic processors. What does FDA do to document training of investigators?
A. Mentor new ones – 30-35 in Atlanta, mostly for bio-terrorism. There has been talk of certification in Drug Inspections using a checklist to judge them. Speaker thinks a certification process is coming. There is always a learning curve. Not sure certification will be adequate. Must remember investigators also visit feed mills, imports, food sites, etc. …. District office wants to know about problems, but the investigators are scared to put anything in writing due to possible retaliation.

Q. Carry-over limits and cleaning – There are different standards for detergents (requirement=none present) and drugs.

1. **10ppm standard**
2. **Look at individual detergents and test down to null**
3. **Max carry over of surfactants**
4. **Shake – no foam=OK**
5. **LD 50 – Oral**

Does the FDA have a position?
A. Either approach can be valid; must look at justification and rationale. There is no single way it must be done. FDA is likely to leave it up to industry to standardize (rather than FDA setting a standard.)

Q. Do training systems, LIMS, SOP management tools need to be Part 11 compliant?
A. Yes, if the are engaged in a GMP function.

Q. When executing a validation protocol, does one need to sign and verify each step/component or would it be OK just to sign off and verify at the end?
A. Sign off and verify on each one as you perform the function (reference CFR21).

Q. If a test was invalidated in error, can we go back and accept the result?
A. If a test was invalidated based on bad judgement, yes, then go fix it. Explain why, what happened, and support these decisions with adequate documentation to avoid future problems.

Q. If a result does not meet an equipment validation/ qualification protocol acceptance criterion, is it still OK to accept the results?
A. If protocol has a spec that is not based on sound science and application of the equipment, it is OK to rationalize the decision to accept the values based on the real acceptance criterion. Document the failure and the justification. However, this must not be a pattern since it will point out to another problem with creation of inadequate validation protocols.

Q. Is there a requirement for minimum batch size for parenteral formulations?
A. No, not even for clinical material.

Q. Does the FDA consider Excel a validated system?
A. No. Spreadsheets must be validated. If a spreadsheet is not validated, use a back up mechanism, such as secondary check. However, why even use the spreadsheet if you have to verify 100% of calculations?

continued on Page 14

continued from Page 13 (Compliance Round Table)

Q. What is your opinion on how much validation of lab methods needs to be performed during product development?
A. It depends on where you are in the development. If data is part of a regulatory filing, then the methods must be validated. Equipment must be validated and calibrated to ensure data is accurate and equipment is functioning properly. If method is not validated, must runs controls to ensure accuracy of test results. Of course, the level of validation during product development is not expected to be as much as with a commercial product. The issue of validation of assays during method development is not a focus of the FDA.

Q. What is the regulatory expectation for inspection of chemical excipient facilities?
A. FDA does not inspect excipient facilities unless it is a component of the drug formulation. The agency expects that companies in the industry will inspect themselves.

Q. Is vendor audit a regulatory requirement?
A. No. Vendor audit is not a requirement but an expectation. The burden is placed on the receiving company to do an audit of a vendor and make sure the item/component is manufactured to an acceptable level of compliance.

Q. What are typical metrics that the FDA looks for?
A. Typically the FDA will look for records of frequent management meetings, check list of investigations, deviations, quality review, etc… The FDA would want to see proof of meetings addressing adverse trends for example. They will also look at the program for internal audits instead of requiring to see the actual internal audit reports.

Q. What is the definition of a "timely" investigation?
A. There is no hard fast rule. Most companies use 30 days.

Q. What is the FDA approach for retests, especially for microbial testing of perishable sample, for example, bioburden testing of in-process samples?
A. Usually, one must have an assignable cause before a retest starts. However, there is a school of thought in the FDA that states that even if the assignable cause is not found, a retest can be done with a well-thought out retest plan. It is also a good idea to have a separate OOS SOP for microbiological testing since the approach to the investigation can be quite different from analytical investigations.

Q. Is there a value in performing a retest on an expired sample?
A. There is a value to further evaluate the original questionable result but it cannot be used as a valid result.

Q. Should a company have a department dedicated to training?
A. There is no requirement for a training department. The expectation is that training must be done up front and not concurrent with an official test. One must have a methodical process. Trainer and trainee must test the material separately, especially if the program involves training with expired materials.

Q. How do you address training during a technology transfer?
A. An analyst participating in a formal tech transfer to the QC lab can be considered trained.

Q. Is there a requirement for annual retraining?
A. If procedure hasn't changed there is no requirement. However, a company must have a requirement for retraining based on history of invalid assays, deviations, etc… Best way is to retrain soon as an issue is observed instead of waiting for an annual retraining.

Cut and keep for your records

PDA Southeast Chapter 2003 Calendar

Tuesday, September 23, 2003, PDA Southeast Chapter Fall Meeting and Vendor Show, McKimmon Center (NEW LOCATION), Raleigh (Off Western Blvd. near NCSU). Registrations will be mailed in August.

McKimmon Center Directions:

Directions: From I-40 traveling east from airport. Take Gorman Street Exit #295. Turn left onto Gorman Street. Go apporoximately 1 mile. McKimmon Center is on the right past Avent Ferry Rd. before Western Blvd.

From I-40 traveling west. Take Gorman Street Exit #295. Turn right onto Gorman Street. Go approximately 1 mile. McKimmon Center is on right past Avent Ferry Rd. before Western Blvd.