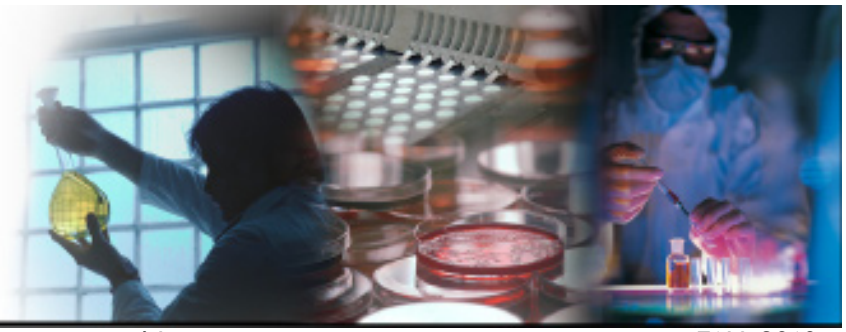
Carolina-South Atlantic Chapter
ENGINEERING PHARMACEUTICAL INNOVATION



Volume 17 · Number 3 Engineering Pharmaceutical Innovation FALL 2010

INSIDE THIS ISSUE

Technical Article Submissions

Publication Opportunities Exist in the Following Areas

- Innovative Technology
- Automation Solutions
- Operational Excellence
- Critical Utilities
- Commissioning and Qualification
- Process Development
- Oral Solid Dosage
- Facility Design
- Contract Manufacturing
- Regulatory Affairs
- Project Delivery
- ... and many more!

Articles should be written for technical professionals in the pharmaceutical, biotechnology, and medical device industries. The author is responsible for the accuracy and correctness of all statements contained in the manuscript (ISPE Carolina-South Atlantic Chapter assumes no liability.) Submission of technical article does not guarantee publication in the eNewsletter. We reserve the right to edit and select all entries. Articles that promote a specific product or company will not be accepted.

Editor's Note

It's hard to believe that 2010 is already over! The ISPE CASA Board of Directors is in full swing planning upcoming events. Make sure that you add Casino Night, CASA Leadership Symposium, and the Technology Show to your calendars.

The Communications Committee will have its first meeting of 2011 on January 13th. We have many objectives to accomplish in the New Year. If you are interested in joining the Communications Committee please contact me directly at megan.crum@merck.com.

We will begin take 2011 advertisements the first week of January. This is an excellent branding opportunity to place a full-color, business-card sized ad in our local newsletter!

I look forward to seeing you all at upcoming local events!

Warm Regards,

Megan Crum

Megan Crum
Communications Chair

ISPE Carolina-South Atlantic Chapter
ENGINEERING PHARMACEUTICAL INNOVATION

2010-2011 Board of Directors

Officers

- **Scott Billman,** *President*
- **David Brande,** *Vice President*
- **Jennifer Lauria Clark,** *Treasurer*
- **Matt Gilson,** *Secretary*

Directors

- **Wendy Haines**
- **Rob Hughes**
- **Jim Murphy**
- **Wes Robbins**
- **Bruce Craven**
- **Eric Mayer**
- **David Smith**

Committee Chairs

- **Megan Crum,** *Communications*
- **Heather Denny,** *Membership*
- **David Knorr,** *Programs*
- **Amy Lineberry,** *Students*
- **Blake Derrick,** *Young Professionals*
- **Alan Tucker,** *Tech Show*

President's Message

By: Scott Billman, ISPE CASA Chapter President

Welcome to another great year with ISPE CaSA. I am excited about the opportunities that are available for us as a chapter and as a new Board of Directors over the next 12 months. Thank you to all of our members that have stayed involved in chapter activities over the summer, including the Durham Bulls game, and the voting in of our new leadership. As the face of our industry changes, and starts to look younger, ISPE is faced with many challenges in the future. That is why one of our key goals for the next year is the further development of Young Professionals as an active committee. ISPE International has recognized this segment of our membership as a focus area for our future growth as a society. Keep a look out for new information on this initiative.

We are fortunate to have an active membership in our events and in our committees. We offer our thanks to the Board members that have completed their terms and served the membership over the past several years. Outgoing President Mark Mathis has provided valuable time and effort in our transitions and is still active on the Board of Directors as he leads our Industry Advisory Council. Mark was also afraid of having too much free time on his hands so he has agreed to be the Co-chair for the ISPE North American South American Affiliate Council (NASAAC). This International ISPE level volunteer position shows us just how dedicated to ISPE Mark is, and has been. Special thanks to our outgoing Board members Lisa Saxon, Kevin White, Shelley Preslar – Technology Show Chair, and Jacqui Roth – Immediate Past President for their years of leadership and personal time to improve the CaSA Chapter.

The chapter hit the ground running this Fall with three events held in August and September. We started off the program year with our annual Planning Session at the RBC Center Arena Club. It's an exciting time at the RBC Center as all of the Caniacs prepare to host the NHL All Star game this year! It was a great turn out of members and students, all participating in discussions about our chapter, the programs we can provide, and the value of ISPE membership. We then rolled right into an Energy Management Forum to discuss the challenges of being green and energy efficient in a regulated industry. Many thanks to the people at Novartis for hosting the event at their beautiful new facility in Holly Springs. The next event was our annual Gala and this year we held it at the Umstead. What a venue to discuss nanotechnology and the future of biotechnology!

The CaSA Chapter is also excited about the future opportunities with our new chapter management firm. FirstPoint Resources has been brought into the group as of August this year. Their large network of services and resources are at the chapter's disposal to help us grow into the future. The main contacts there are Peter Kralka and Casey Hinson and they can be reached at (919) 787-5181 or by email at pkralka@FirstPointResources.com, chinson@FirstPointResources.com.

Led by the Board Officers – David Brande, Vice President, Jennifer Lauria-Clark, Treasurer, and Matt Gilson – Secretary. our active Board of Directors is hard at work planning the future events, newsletters, and membership activities. Our At-Large Board Members returning are Wendy Haines, Rob Hughes, Jim Murphy, and Wes Robbins. Our new members are Bruce Craven, Eric Mayer, David Smith, and Blake Derrick, and we welcome them to the Board. Below is a quick highlight of each committee and their goals. Feel free to contact any of the Board Members or our Chapter Manager for opportunities to get involved. It's the active

participation of the membership that will provide the long term value of ISPE.

Programs Committee
Led for the second year by David Knorr the Programs Committee is hard at work planning educational events for the chapter. In addition to the 2 programs already held this year they are working on an Automation Forum, a joint event with ASHRAE, and developing more opportunities to learn from and network with your peers in the industry.

Communication Committee
Megan Crum is leading the Communications Committee for the second year. Her committee works on providing up to date information about the chapter and pertinent technical articles in the quarterly newsletter. A new initiative the Communication Committee is taking on involves website updates and overall chapter communication. If you are interested in helping out please contact Megan.

Technology Show Committee
Alan Tucker takes over the leadership of the Technology Show this year. Alan leads a seasoned group of volunteers who put on the chapter's biggest event of the year. We continue to hold the event at the RBC Center to accommodate the great turnout. This is one of the busiest committees with lots of planning to do so contact Alan if you are interested in helping.

Student Development Committee
Amy Lineberry continues her leadership of the Student Development Committee for the second year. Her committee's focus and drive for student chapter development and inclusion is the best I have ever seen. The dedication that CaSA has to the student chapters in the area is very evident as we continue to add new schools and send the most students to the ISPE Annual Meeting than any other chapter.

Young Professionals Committee
Blake Derrick was elected to the Board of Directors this year to lead the development of our newest committee, the Young Professionals Committee. Blake and his committee have their work cut out for them as they try to develop programs and events targeted at the professionals that are new to our industry. Contact Blake to get involved in this new, energetic group.

Membership Committee
Heather Denny is in the second year of leading the Membership Committee. She and her group continue to plan all of the chapter's fun events like the Durham Bulls game, Casino Night, and the always popular Golf Outing. Keep an eye out for some exciting venue changes this year!

As you can see there is a lot going on in the CaSA Chapter. We hope to see everyone getting involved in the multitude of activities and committees to help grow the value of ISPE to the membership. If you were at the annual meeting in Orlando you might have met some of our students -- they were facilitators at many of the educational seminars. When you meet them closer to home, introduce yourself and help foster the next generation of ISPE CaSA members.

Chapter Announcements

Event	Location	Date
Leadership Symposium	McKimmon Center NCSU, Raleigh, NC	05 Feb 2011
Casino Night	The Capital City Club Raleigh, NC	19 Feb 2011
Technology Show	RBC Center	05 Apr 2011

Welcome New Members!

Kurt C. Anderson
Jennifer Aquino
Adam J. Barlow
Elisabeth Bernitt
Himanshu Bhattacharjee
Anibal Borroto
Jeff Brown
Chase Buckner
Kwanita Burwell
Toynette Coachman
Ann M. Coore-Scott
Lourdes Cordeiro-Piloto
David Denoo
Blake F. Derrick
Brett Easterling
Melissa M. Endejann
Gayle A. Flynn
Eric W. Franson
Austin A. Gallardy
Inge S. Garrison
David R. Glunt
Russell Gold
Tom Golden
Malikah Greene
Andrew J. Hill
Melanie Hocutt
Ashley Hogan
W Paul Jackson
Joan Johnson
Kenny Johnson
Kevin Johnson
Carla S. Johnstone
David D. Jones
Kristopher Kelly
Peter Kralka
Miss Christie A. Ku
Patricia Lee
Maura C. Leonard
Bobby W. Lewis
Ginaya Littlejohn
David W. Long
Kelsey C. Long
David A. Loy
Charles Jon Lyerly
Syreeta Dawn Lyons
Ashley-Charli McCall
Eddie McDaniel
Thomas McLean
Joe S. McNabb
Sarah Mecouch
Samuel A. Millard
Doug Miller
Sabrina Moore
Billy R. Morris
Jason A. Morton
Philip M. Myers
Quang Nguyen
Robert C. Oldham
Natalie G. Patterson
Benjamin A. Perkins
Bradley P. Phillips
C Powell
Pamela Prescott
Jessica A. Richards
Juan C. Rubio
Sravani Sayyaparaju
Max Scates
Darpan H. Shah, M.S.
LaShaya Smith
Lee Smith
Patrick R. Snipes, II
Jonathan Spivey
Kyle T. Stoker
Chad Sunstrom
Jasmine C. Taylor
Jason E. Thomason
Justin E. Thompson
Lisa Tinsley
Vishal M. Toprani
Timothy G. Tullis
Carlos Uribe
Nicolo Eddie Vargas
Alan B. Villanova
Robert Carl Wood, III
Jarrett Wyatt
John D. Youngblood
Hai N. Yu
Paul Z. Zahorchak
Yong Zhang
Lisa A. Zoppo

2010 ISPE CASA Annual Planning Session

By: Jennifer Lauria Clark, ISPE CASA Chapter Treasurer
Yonkers Industries, Inc.

Once again CASA members gathered to share their ideas and suggestions for another successful year. On Thursday August 26, about 80 CASA ISPE members joined together at the RBC Center in Raleigh, NC to exchange ideas and network with each other. The outgoing board was recognized for their efforts over the past year that helped keep our chapter strong. The incoming board was introduced and challenged to make this year just as successful as years past.

Each committee chair described to the membership what their committees are responsible for in order to keep the chapter going and what their needs are for the upcoming year. We have six committees and one of them needs you! Our committees include Programs (Educational Events, Annual Gala), Membership (Toys for Tots, Casino Night, Golf Tournament), Students (Poster Competition, Student Chapters, Leadership Symposium), Young Professionals (Networking and Educational Events), Technology Show (Tech Show), and Communications (Newsletter and Website).

If you are interested in serving on a committee or just helping with a certain event such as the Leadership Symposium, Casino Night, Golf Tournament, planning an educational program, etc, please contact the respective committee chairs.

Thank you to everyone who has given their time and experience to make this another successful CASA Annual Planning Session

4th Annual Fall Gala

By: *Martin E. Rock, P.E., J.D., LEED-AP*
ISPE Carolina-South Atlantic Chapter
Past President & Programs Committee member

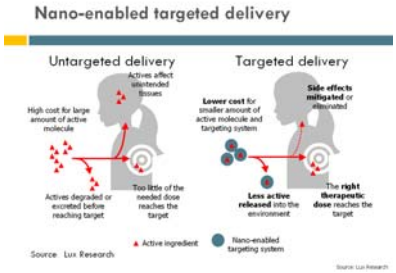
Did you know there are 528 bioscience companies in North Carolina? Or that both NC State and UNC-Chapel Hill are both ranked in the top 5 nationally for nanotech commercialization? (Other major universities in our Chapter service area including Georgia Tech, University of Florida, Vanderbilt University, Duke and Emory are also recognized leaders in the nano field.) These were some of the "fun facts" ISPE – CASA Chapter members & guests learned during this year's gala dinner event on September 30, 2010 at the Umstead Hotel and Spa in Cary, NC.

Fred Miesowicz from Argos Therapeutics and Brooks Adams from the North Carolina Center of Innovation for Nanobiotechnology (COIN) presented their views on the current status and outlook for biotechnology. COIN is a non-profit launched in June 2009 to accelerate & promote commercialization of nanobiotechnology and Argos is a private biotechnology company headquartered in Research Triangle Park. Argos has clinical trial programs in metastatic renal cell carcinoma (RCC) cancer, human immunodeficiency virus (HIV) and systemic lupus erythematosus (SLE).

Fred Miesowicz
Argos Therapeutics

Brooks Adams
COIN

Both presenters discussed targeted therapies from slightly different perspectives. (Argos uses personalized dendritic cell-based technology.) Targeted therapies give medical personnel better ways to tailor treatments. Eventually, treatments may be individualized based on the unique set of molecular targets produced by the patient. Targeted therapies also hold the promise of being more selective for target cells than for normal cells, thus harming fewer normal cells, reducing side effects, and improving quality of life.



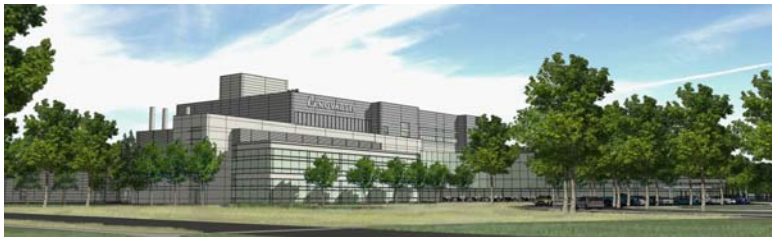
Targeted therapies also have some limitations. Chief among these is the potential for cells to develop resistance to them. In most cases, another targeted therapy that could overcome this resistance may not be available. For this reason, targeted therapies may work best in combination, either with other targeted therapies or with more traditional therapies.

We appreciate our presenters taking time to share their perspectives on the future of biotechnology. Special thanks also to the Chapter Programs Committee volunteers and to our Chapter managers, First Point Resources, for all their help in organizing this year's gala dinner. (*The presentation slides are available at the Chapter website***.)**

Energized for the Future

2010 ISPE CASA Energy Management Forum

By: *Martin E. Rock, P.E., J.D., LEED-AP*
ISPE Carolina-South Atlantic Chapter
Past President & Programs Committee member



An impressive team of knowledgeable speakers, a brand new $1 billion facility, and a lively audience combined to make the ISPE Carolina-South Atlantic Chapter, 2010 Energy Management Forum a success. The Forum was held on September 16, 2010 at the recently completed Novartis Vaccines and Diagnostics vaccine manufacturing facility located in Holly Springs, North Carolina. The Chapter attendees had the opportunity to learn from four different technical presentations by some of the major pharmaceutical operating companies in the area.

Energy management has emerged as a hot topic within the industry as a "win-win" strategy for both improving operating margins and striving for environmental excellence. State-of-the-art technology and notable engineering applications, even including solar power systems, have combined to demonstrate the effectiveness of these strategies within the pharmaceutical/biotechnology operating environment.

The Novartis facility was designed to manufacture bulk and finished product (pre-filled syringes) for seasonal and pandemic influenza vaccines. The manufacturing process will include advanced technologies for flu vaccines utilizing cell culture, instead of conventional technology using fertilized chicken eggs, via two cell culture lines and two downstream processing (purification) lines.

The facility will ultimately have annual bulk seasonal flu capacity of 50 M doses (trivalent) or 150 M doses (monovalent) within 6 months after declaration of a pandemic and meets biosafety level 2+ with capability to upgrade to BSL3. Special thanks to Jamie Iudica, Senior Director of Technical Operations, and to the management & staff at the Novartis-Holly Spring site for hosting this event.

The ISPE-CASA Energy Management Forum was hosted by Novartis, Holly Springs, NC, and the event was held in the cafeteria area. The window walls in this part of the building help to harvest natural lighting

Novartis not only hosted our event, but Lee Willmon, Head of Health, Safety and Environment and Alexander Mitrovic, PE, CEA presented specific examples of how Novartis has successfully improved energy efficiency by 22% since 2006. One interesting example was the heat recovery chiller system at the plant.

A heat-recovery chiller uses less total energy than separate cooling and heating equipment by taking advantage of "free" condenser heat that would otherwise be lost or wasted through the cooling towers. In effect, a heat-recovery chiller lets the facility do "double-duty"—cooling and heating with the same piece of equipment. This is more economically and environmentally friendly than burning fossil fuels or using electric heaters. Energy managers and engineers refer to this as increasing the

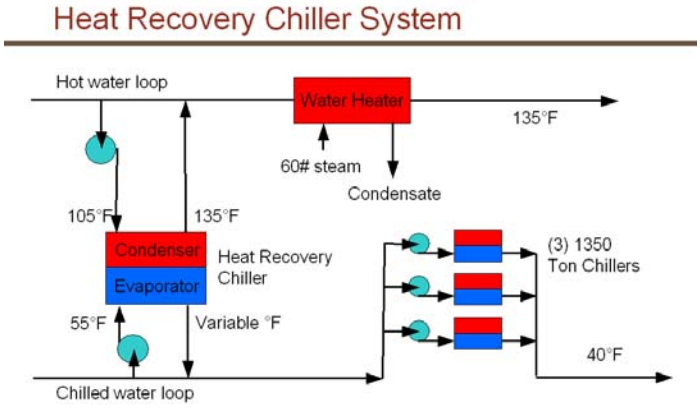
"coefficient of performance" (COP) of the equipment since the chiller system is simultaneously providing heating and cooling.

Novartis reported benefits of this technology including the following:

Annual calculated savings:

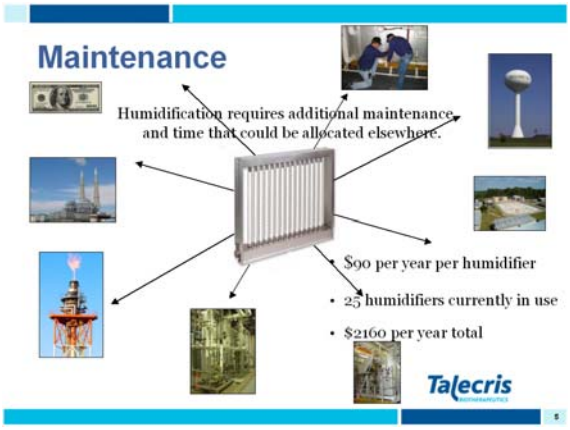
-Saved $750,000 in utility bills
-Eliminated 7,240 tons of CO_2 emissions
-Avoided using 13,724,000 gallons of supplied water
-Reduced chemicals for water treatment

- *Boilers are not needed to provide heating hot water for the site.*



Schematic diagram of the heat recovery chiller system at Novartis
Note: The heat recovery chiller is not piped to a cooling tower. All heat must be rejected to the heating hot water loop.

Wayne Beaver at Talecris Biotherapeutics provided another interesting technical presentation at the Forum. Plant engineers at Talecris found that significant capital and operating costs could be avoided by reducing humidification requirements in accordance with ASHRAE standards without adversely affecting the plant's environmental monitoring data. This resulted in direct savings of $340,000 per year in avoided operating costs and $7 million in avoided capital costs.



Talecris presented a case example yielding over $7 million in avoided costs.

A presentation from GSK (David Twellman) described an interesting photovoltaic solar power application. The rooftop system at GSK is able to provide power to the administrative headquarters building.

The rooftop solar power system at GSK, Research Triangle Park campus includes a web interface allowing the public to see the power production and CO2 emissions avoided.

Another presentation from Merck/Diosynth (Matthew Franks) described Lean manufacturing & energy management principles with actual operating examples from the Morrisville plant. In case you were unable to join us, you can view the presentation slides at the following web link:

http://www.ispe.org/cs/carolinasouth_atlantic_chapter_section/carolinasouth_atlantic_chapter_presentations

Again, we thank Novartis for their hospitality, and we thank all of our sponsors and presenters for their help in making this event a very special and successful educational opportunity for our Chapter.

Announcement: CASA Leadership Symposium

Come out and join us for our fifth annual CASA Career Leadership Symposium, formerly known as the Student Leadership Forum. The committee is very excited about the new topics being introduced for the 2011 workshop. There will be more of a Young Professional emphasis during the workshop including discussions on work place ethics, guidance on how to prepare for your performance reviews, how to run a meeting effectively, conflict resolution, and more. We would like you to save the date of Saturday February 5, 2011 from 08:30am to 3:30pm.

This event will be held at the NC State McKimmon Center in Raleigh, NC. There will be students from local universities participating, young professionals, and professionals attending the event. There will be a networking reception Friday night February 4, 2011 for those interested and dinner after the event on Saturday night at a local restaurant. If you are interested in sponsoring, please contact jclark@yonkersindustries.com.

This is a great event to get your company involved with recruiting new, young talent. CASA has a terrific talent pool of current and future employees looking for great companies to join. Professionals are needed the day of the event to mentor and discuss topics at round tables with the young professionals. The Saturday daytime event is free to all participants. Breakfast and lunch is included.

We look forward to another successful event for CASA in February and hope to see you there! If you would like to volunteer to help plan the event, set up the day of the event, sponsor, mentor, or have any questions, please contact jclark@yonkersindustries.com.

Guide for US FDA-Regulated Organizations

"How to Avoid and Respond to FDA Criticisms—Form 483 Letters —for Temperature, Humidity and other Controlled Environments"

By: **Ken Appel**, *VP of Regulated Markets Veriteq, a Vaisala company*

No cGMP manufacturer wants to receive a Form 483 letter ("Notice of Inspectional Observations"). In such stringently controlled industries as pharmaceutical/biotechnical development, manufacturing and warehousing, receiving a list of deficiencies can feel like a heavy blow to your quality system. Worse, with the 2009 increase in enforcement staff[1] and the September 2009 change to the response time—now 15 days—the FDA appears to be ramping up its enforcement mandate.[2]

The following article shows three excerpts from some of the more common "observations" noted in Form 483 Letters during 2008-2009. (The names have been left out in this article, but are a matter of public record).[3] Each of these deviations involved environmental conditions (temperature, humidity, etc.) in a variety of cGMP settings; they range from failure to properly validate containers for Human Cell & Tissue Products to a lack of temperature records in an aseptic processing area of a drug manufacturing facility. None of the deviations excerpted here are unique, but all are avoidable.

After the excerpts, we'll outline some best practices of a 483 response, providing you with a 10-point checklist that should make that 15-day time limit more manageable, and some links for further research. Finally, we'll look at ways to simplify and automate monitoring, alarming and reporting on FDA regulated environments. Options range from low-tech manual methods, to hybridized systems that combine written and electronic methods of documentation, to fully automated systems.

Many opportunities are available to tighten up documentation of controlled environments with modern technology.

Sample Deviation #1
To a Contract Pharma manufacturer:

"Requirements for stability testing of drug products are not being met. For example, you do not have, as part of the storage condition, any documentation that stability samples are maintained at the designated temperature [21 CFR 211.166(a)(2)]; and you do not have appropriate stability data to support the 4 year expiration date for the product. [21 CFR 211.166(b)]"

Sample Deviation #2
To a blood bank:

---

[1] Parts of this article were sourced, with permission, from two documents **1) "FDA 483 Responses—Compliance Considerations"** by Richard Poska and Ballard Graham, as published in the *Journal of Validation Technology,* Winter 2010 — available with subscription at: http://www.gxpandjvt.com/ivtnews/templates/IVTNews.aspx?articleid=1896&zoneid=27
and the FDA Presentation **2) "Writing An Effective 483 Response"** presented by Anita Richardson, Associate Director for Policy, Office of Compliance & Biologics Quality at the 5th Annual FDA University RI Pharma Conference, January 2009 available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM102921.pdf

[2] **"FDA's Enforcement Crackdown To Increase Inspections, Delays",** *Drug GMP Report* - Issue No. 210, January 2010

[3] From the FDA's Warning Letter web page: **"Inspections, Compliance, Enforcement, and Criminal Investigations"** http://www.accessdata.fda.gov/scripts/warningletters/wlSearchResult.cfm?filter=temperature&sortColumn=&qryStr=21+CFR+Part+11)

"Failure to have quality control procedures and follow those procedures for periodic tests of containers to maintain proper temperature...as required by 21 CFR 606.160(b)(5)(iv)..."

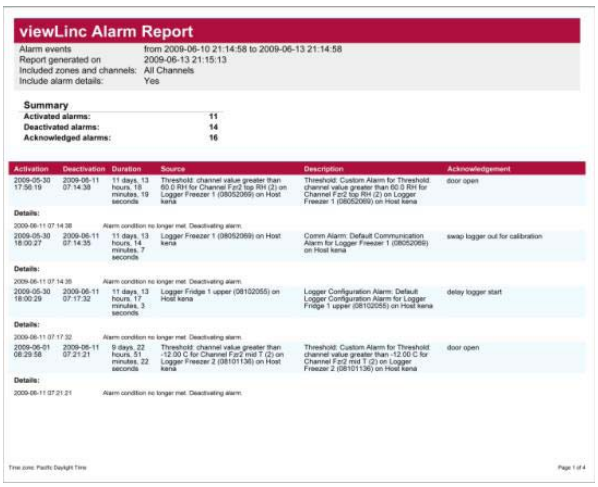
There must be documented evidence at any point in time that an environment was within its recommended specifications.

Sample Deviation #3

To a major manufacturer of OTC Pharmaceuticals:

"Failure to establish and maintain procedures to adequately control environmental conditions, as required by 21 CFR 820.70(c). Specifically, temperature conditions within the aseptic processing area are not being documented to ensure such conditions are consistently within established specifications...

For example, during the inspection we observed that your firm was recording the relative humidity (RH) in the processing room, but not in the sterilization chamber. We also observed that your firm was not maintaining or reviewing the temperature recorder charts generated during your sterilization process of [product x]..."



viewLinc Alarm Report

Alarm events: from 2009-06-10 21:14:58 to 2009-06-13 21:14:58
Report generated on: 2009-06-13 21:15:13
Included zones and channels: All Channels
Include alarm details: Yes

Summary
Activated alarms: 11
Deactivated alarms: 14
Acknowledged alarms: 16

Activation	Deactivation	Duration	Source	Description	Acknowledgement
2009-05-30 17:56:19	2009-06-11 07:14:38	11 days, 13 hours, 18 minutes, 19 seconds	Threshold: channel value greater than 60.0 RH for Channel Fzr2 top RH (2) on Logger Freezer 1 (08052069) on Host kena	Threshold: Custom Alarm for Threshold: channel value greater than 60.0 RH for Channel Fzr2 top RH (2) on Logger Freezer 1 (08052069) on Host kena	door open
Details:					
2009-06-11 07:14:38		Alarm condition no longer met. Deactivating alarm.			
2009-05-30 18:00:27	2009-06-11 07:14:35	11 days, 13 hours, 14 minutes, 7 seconds	Logger Freezer 1 (08052069) on Host kena	Comm Alarm: Default Communication Alarm for Logger Freezer 1 (08052069) on Host kena	swap logger out for calibration
Details:					
2009-06-11 07:14:35		Alarm condition no longer met. Deactivating alarm.			
2009-05-30 18:00:29	2009-06-11 07:17:32	11 days, 13 hours, 17 minutes, 3 seconds	Logger Fridge 1 upper (08102055) on Host kena	Logger Configuration Alarm: Default Logger Configuration Alarm for Logger Fridge 1 upper (08102055) on Host kena	delay logger start
Details:					
2009-06-11 07:17:32		Alarm condition no longer met. Deactivating alarm.			
2009-06-01 08:29:58	2009-06-11 07:21:21	9 days, 22 hours, 51 minutes, 22 seconds	Threshold: channel value greater than -12.00 C for Channel Fzr2 mid T (2) on Logger Freezer 2 (08101136) on Host kena	Threshold: Custom Alarm for Threshold: channel value greater than -12.00 C for Channel Fzr2 mid T (2) on Logger Freezer 2 (08101136) on Host kena	door open
Details:					
2009-06-11 07:21:21		Alarm condition no longer met. Deactivating alarm.			

Time zone: Pacific Daylight Time

Page 1 of 4

Controlling environmental conditions is more often about being notified of a problem than the actual failure itself.

There is no regulatory requirement to respond to a 483. According to the agency, they are merely *"…inspectional observations, and do not represent a final agency determination regarding your compliance."* Sort of like an offer to help you with your compliance concerns. However, not responding quickly and carefully will most likely result in further investigation. In addition, all Warning Letters are posted on the FDA's site[4] in html format and are therefore indexed by search engines. Once you receive a 483, all anyone needs to do is type [Your Company/Lab's Name] + FDA (or +483) into the search box, and there you are.

10 ½ Tips for the Right Response

Your initial response must do three things: it must establish credibility, it must demonstrate acknowledgement of the observations and an understanding of the specific requirements referenced, and it must show that your facility is committed to corrective actions, any and all.

You can show commitment by working cross-departmentally; include a statement from all relevant department heads that briefly but specifically addresses each observation. Each observation needs to have a corrective action—either planned or accomplished—and it must be feasible and deliverable within a predetermined time-frame.

Here are some tips—some simple, some in depth—for responding appropriately to 483 letters:

1. Get your response in on time and in writing. You have 15 days, so ensure that final proofing and substantive editing is done at least by day 10.

2. In the first paragraph of the response letter, be explicit in your understanding of and desire to comply with FDA regulations.

3. Respond *individually to each item* that was

[4] See the ORA FOIA Electronic Reading Room at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

addressed in the Warning letter. Be specific. Do not try to solve all issues in one paragraph or your response may be rejected, prompting further action from the FDA.

4. Respond by importance – that is, respond individually to items most likely to impact product quality.

5. Be detailed yet concise in each response. Outline how each deficiency will be corrected, *and when,* rather than how the deficiency came to be. Provide documentation of a corrective action commitment from the person responsible for it.

6. Use positive statements; avoid language that implies fault. Address each item in the form 483 as an opportunity to fine-tune the quality and compliance systems and personnel.

7. Include reference to how you will be forwarding evidence to support the correction. For example, —<Company X>will use Veriteq's validated monitoring and alarming system to provide reports on temperature recordings taken at 10 minute intervals month-by-month. ‖ Product specifications and protocols of any new systems can be provided or offered in support of the corrective action plan.

8. If the inspector noted something that you feel was an isolated incident, document this fact and note it in your response. Be sure your data is complete and accurate. If you find some of the observations were in error after receiving the 483, there is a formal dispute resolution process outlined in the agency's "Guidance for Industry - Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP."[5]

9. Be proactive. Reassess your internal compliance programs — Why were 483 deficiencies not detected internally? Mention this in your response letter, noting your commitment to QC/QA audit management. The definitive guide to what FDA inspectors are looking for (at least in theory) is the agency's "Investigations Operations Manual" accessible at: http://www.fda.gov/ICECI/Inspections/IOM/default.htm

10. If you need clarification, seek it—in writing and from the correct party. Ideally, when the investigator gave you the Form 483 after the inspection you asked a lot of questions to clarify each observation. Try to be sure you are clear on each observation *before* the inspector leaves your facility and make notes while he/she is explaining the observations. If your questions involve policy, contact the FDA headquarters—don't contact your local FDA because policy is set at HQ.

10.5 You may need an industry expert. There are many companies who specialize in creating and implementing regulatory strategy, whether from the ground up or from your existing quality and regulatory systems. If it's worth doing, it may be worth hiring someone who knows how to do it really well. As regulatory compliance issues grow more complex, many companies have been created to provide solutions in common compliance areas like: response to agency queries and help with agency meetings, regulatory gap analysis & remediation, internal GLP/GMP auditing and pre-approval inspections.

Ways to Avoid 483s with Audit-Ready Environmental Monitoring

Ideally, your regulated environments and equipment are always in full compliance with FDA regulations. An automated monitoring and alarming system providing high accuracy data at the point of measurement with back-up recording — can make your QA/QC efficient, optimal and ready for any critical evaluation, internal or

[5]http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070279.pdf

external. The continuous records that this type of system should provide could help be part of your detailed response to quality concerns outlined in a Form 483 letter.

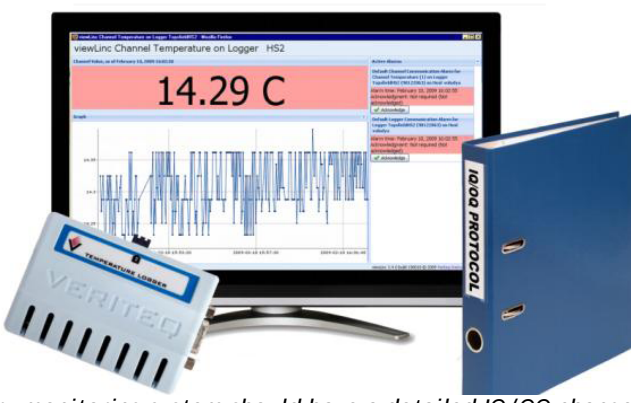
For example, in the 483 excerpt of the CMO, which noted that "*documentation that stability samples are maintained at the designated temperature*" A validated monitoring and alarming system would provide secure, gap-free temperature data recording. Data loggers with long-life batteries (up to 10 years) can continue to record temperature at the point of measurement, rendering environmental data immune to network or power failures.

	Channel Fzr1 fnt T (1) on Logger Freezer 1 (08062069) on Host kena (C)	Channel Fzr1 rear T (1) on Logger Freezer 2 (08062119) on Host kena (C)	Channel cpeo fzr1 T (2) on Logger Freezer 2 (08101138) on Host kena (C)	Channel cpeo fzr2 T (1) on Logger Incubator 1 (08101138) on Host kena (C)	Channel cpeo fzr2 T (1) on Logger Incubator 2 upper (08102066) on Host kena (C)	Channel Fzr1 RH (2) on Logger Room 1 (08062119) on Host kena (RH)
2009-07-20 08:11:43	-24.84 *	-26.78 *	-70.51 *	70.51 *	70.80 *	70.80
2009-07-20 08:12:44	-24.84 *	-26.86 *	-70.22 *	70.22 *	70.80 *	70.80
2009-07-20 08:13:43	-24.84 *	-26.71 *	-69.71 *	69.71 *	70.22 *	70.22
2009-07-20 08:14:43	-24.90 *	-26.78 *	-69.15 *	69.15 *	69.54 *	69.54
2009-07-20 08:15:43	-24.90 *	-26.78 *	-71.21 *	71.21 *	71.51 *	71.51
2009-07-20 08:16:43	-24.97 *	-26.78 *	-71.15 *	71.15 *	71.93 *	71.93
2009-07-20 08:17:43	-24.97 *	-26.78 *	-70.62 *	70.62 *	71.39 *	71.39
2009-07-20 08:18:43	-24.97 *	-26.78 *	-70.05 *	70.05 *	70.62 *	70.62
2009-07-20 08:19:43	-25.04 *	-26.78 *	-69.59 *	69.59 *	69.93 *	69.93
2009-07-20 08:20:43	-25.04 *	-26.86 *	-70.21*	70.01 *	71.32*	70.95
2009-07-20 08:20:47	-25.02*	-26.77 *	-71.09 *	71.09 *	71.45 *	71.45
2009-07-20 08:21:43	-25.04 *	-26.93 *	-70.80 *	70.80 *	71.45 *	71.45
2009-07-20 08:22:43	-25.04*	-26.86 *	-70.28 *	70.28 *	70.86 *	70.86
2009-07-20 08:22:44	-25.04 *	-26.93 *	-70.98*	70.98*	70.33*	70.73

Monitoring, alarming and reporting are only as good as the measured data—accurate and continuous.

Regarding the blood bank 483 example, the storage units can be validated with the same equipment used to monitor. Self-contained data loggers with internal sensors, memory and battery can be equipped for "periodic testing" or mapping the temperature distribution of the containers.

In regard to the observations on the OTC Pharmaceutical manufacturer, the challenge of not having adequately documented temperature conditions would be solved by following the detailed IQ/OQ and SOPs provided with the monitoring, alarming and reporting system.



Every monitoring system should have a detailed IQ/OQ change control document make validation a straightforward process.

Some organizations compliant with GMP still use chart recorders or manual methods to track temperature and humidity. The issues with these methods are beyond the scope of this article, but as more facilities automate processes within quality assurance and regulatory compliance, relying on older technologies is and will continue to be problematic. The FDA, with its "strong recommendations", cannot insist that organizations upgrade to any given technology. But, a commitment to using industry-best instrumentation and systems in FDA-regulated research and manufacturing processes can stave off misgivings about a facility's commitment to quality.

Student Chapters Update

By: Amy Lineberry, ISPE-CASA Student Affairs Chair

The Student Chapters were very active over the summer and have kept the momentum going for the new ISPE year. I would first like to welcome a new student Chapter. East Tennessee State University emailed ISPE HQ in mid-August and became an official chapter at the beginning of October. This is the quickest I have ever seen a chapter formed. They are a very enthusiastic group of students. We have also had a dormant chapter come back. North Carolina A&T is now once again an active chapter. For those of you counting, this gives us eleven schools in our CASA chapter.

The students have not only been actively preparing and having meetings and events at each school but also prepared for the trip to the Annual Meeting in November. This year CASA, with help from the students, was able to take 18 students to the Meeting. This includes the two Poster Winners who won their categories in March. This was the largest group of students CASA has ever funded to attend the Annual Meeting.

Young Professionals Update

By: Blake Derrick, CASA YP Committee Chair

The ISPE Young Professionals group finished out the summer season strong with a fun bowling event in August, at which over twenty ISPE Young Professionals gathered together for an evening of networking at Pleasant Valley Lanes in Raleigh, NC. We had an excellent turn-out and it was great to participate in conversations among industry professionals from several local biopharmaceutical firms. With a majority of the attendees being first-time participants in the group, it was encouraging to see new relationships form and opportunities to meet colleagues from various organizations.

As the Fall Season has come into full swing, the Young Professionals are currently expanding the leadership team and beginning to organize some exciting events and programs for the upcoming ISPE calendar year. We are already currently in the infancy stage of developing a mentoring program that would provide an organized structure to connect the next generation of ISPE professionals with industry veterans within ISPE-CASA. In the same way, we also hope to provide mentoring opportunities from the Young Professional community to local students interested in learning about pharmaceutical careers and transitioning from the classroom to the workplace. We also look to expand our involvement with all ISPE members by partnering with other CASA programs and developing YP events available to all of ISPE-CASA.

ISPE CASA Chapter E-Newsletter Ads

Newsletter Ads Work for your Business!

Our Chapter produces four e-newsletters per year, and we depend on the support of our advertisers. We send out the newsletters via e-mail and via Web link to all of our Chapter Members throughout the Southeastern U.S.

That means you get targeted access to top-notch pharma, biotech, and bio-science professionals and managers. These newsletters are also posted on our **Web site** so your ad can be accessed by interested visitors to our site.

Best of all, the cost is only $500 for your full color, business-card-sized ad for four insertions. That's only $500 for targeted advertising in full color for an entire year!

Ask About HOT LINKS!!

Would you like to have targeted customers simply click on your ad and get right to your Web site?

A hot-link can be added to your ad, connecting readers directly to your company Web site for an additional $500.00 for a whole year.

If you are interested in advertising with the ISPE CASA e-newsletter, please our chapter manager at:

Peter Kralka, Chapter Manager
1500 Sunday Drive, Suite 102
Raleigh, NC 27607
pkralka@FirstPointResources.com

You will be notified via e-mail or telephone when your advertisement has been accepted by the ISPE CASA Communications Committee and asked to submit your advertisement digitally.

Full-color business card-sized ads (3.5" x 2") may contain your logo or other artwork. Artwork should be sent directly to the committee chair:
ispe_casa_communications@yahoo.com

We ask that your text be no smaller that 12pt so that the text is easily readable in the electronic format. PDF, JPEG, or TIF formats are easiest for us to work with. Space is limited, sign up today!

ISPE Carolina-South Atlantic Chapter Newsletter

1500 Sunday Drive, Suite 102
Raleigh, NC 27607
Tel: 1-919/861-4531 • Fax: 1-919/787-4916
ispe_casa_communications@yahoo.com

EDITORIAL POLICY

Articles should be written for technical professionals in the pharmaceutical, biotechnology, and medical device industries. The author is responsible for the accuracy and correctness of all statements contained in the manuscript (ISPE Carolina-South Atlantic Chapter assumes no liability.) Manuscripts should be forwarded to a Member of the Communications Committee at ispe_casa_communications@yahoo.com for review 30 days prior to publication. A brief three to four sentence synopsis of the article, as well as a brief biographical statement about the author that includes educational background, title and job affiliation, job responsibilities and major areas of accomplishment must accompany the article.

Got News?

Send it to:
ISPE_CASA_COMMUNICATIONS@YAHOO.COM
Entries should be brief and be of general interest to the readership. Entries must include a name and telephone number for verification purposes. We reserve the right to edit and select entries.

A word to the ISPE CASA Newsletter advertisers, thank you all for your continued support, without it we could not be able to have the wonderful support staff to get our ISPE CASA Members the news in such and timely and professional fashion. If you have updates to your advertisements or find any other error, please contact us so that we can serve you better.