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Equipment Maintenance, Calibration and Cleaning:
Often Overlooked, but Never Forgotten!

Webinar

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Speaker: Kenneth Christie, COO, VTS Consultants, Inc.

Operator: Hello and welcome to "Equipment Maintenance, Calibration and Cleaning Programs: Often Overlooked, but Never Forgotten!" This webinar is being presented by FDAnews. By now the main registrant at each dial-in site should have received an email with our speaker's presentation. If not, you may download it from the announcement of this webinar on our website, fdanews.com.

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As a reminder, this call is being recorded and will be available as an audio CD and transcript package by calling FDAnews at (888) 838-5578 or visiting our website, fdanews.com. I would now like to introduce our speaker.

Kenneth Christie is the COO of Consulting Services at VTS Consultants, Inc., and has more than 25 years of experience in the areas of manufacturing of sterile products, quality assurance and validation management. Prior to becoming the Chief Operating Officer for VTS, Mr. Christie spent 13 years with the Parke-Davis Sterile Products Division of Warner-Lambert where he served as manager of the Validation Department for eight years. Mr. Christie also managed contracted validation personnel and defended all corporate validation practices to regulatory agencies such as CBER, CDER and the United Kingdom's MHRA Division. Mr. Christie also spent seven years working for Wyeth Laboratories Sterile Biological Vaccines Division of American Home Products as a manufacturing supervisor. He has a B.S. degree in biology with a chemistry minor and holds an executive master's degree in business administration from Michigan State University.

I'll now turn over the floor to Mr. Christie.

Christie: Thank you very much and depending on where everyone is calling in from, either good morning or good afternoon. Before we get started, just a few things. As mentioned, even though there will be a question-and-answer period at the end of the presentation, feel free if you want to ask a question during the presentation using the Chat box. As they come in, I will try to answer them. Otherwise, if you feel more comfortable to wait at the end, that would be fine.

The other thing I'd like to talk about before we get started is within the next 75 minutes, we are certainly not going to cover all of the details that companies are faced with with regards to these three programs:

Christie (cont.): maintenance, calibration and cleaning, so basically what we will try to accomplish is to use this presentation as a template to use and learn about No. 1, the regulatory requirements for these three programs; to talk about current industry practices which a lot of people like to find out so they can decide whether or not they're doing too much or too little; and then, also to talk about common deficiencies and by covering those three areas, you can then audit your own programs and practices and evaluate them in terms of where you need to improve upon it or where you need to implement things if they're not already in place.

The second thing is during the course of this presentation, I will be giving you different examples, case studies, and they are based on my 10 years of dealing directly with the FDA auditors, with third-party customers and also with issues that I have seen with clients that I am currently working at, so I try to bring in actual examples. I will not use or mention the names of clients or other companies whose example I might use unless I actually worked there from my time at Parke-Davis as mentioned at the beginning of this webinar.

With that, we'll get started. As the title indicates, equipment maintenance or preventative maintenance programs, calibration and cleaning, they are sometimes, or I should say often, overlooked by companies and never forgotten from the standpoint of a regulatory auditor. As the first slide shows, those three programs involve a lot of paperwork and often a lot of frustration in making sure that they are getting done, that they are properly documented and the level of detail is what inspectors expect to see in terms of being assured that operators know what they have to do and when.

With that, we're going to have three major topics that are going to be discussed over the next 75 minutes. They include the regulatory requirements for all three programs. This is important to know so that companies understand why they need to have these programs in place. The regulatory requirements will tell you what the expectations are, but one of the things that all companies must realize, the regulations that we're going to talk about do not tell you how to get to the endpoint, meaning yes, they will tell you you have to have a calibration program that is performed on a routine basis. They don't define what routine means. They don't define how you're supposed to write the procedure. They leave that up to you to decide and then to defend if you are questioned about it.

Second main topic that we're going to cover are the issues associated with frequencies, operational limits and trending of results. Again, the three things that an auditor will look for once he or she starts looking at these programs and we're going to cover other issues with these programs that auditors like to see and talk about the reasons for it.

Then, the final topic, we're going to review the common deficiencies that are cited for each of these programs during audits. In any training that I give or any webinar that I present, I always try to incorporate current deficiencies because it lets you know what auditors are focusing on and what auditors are finding to be deficient with current company practices.

One of the best things in terms of preparing for an audit or even doing audits internally of your own programs, if you know what the deficiencies are out there and what are the common findings, that should be your first point of reference in terms of reviewing your own programs, procedures and whatever it might be because FDA auditors themselves are taught to be made aware of what the current findings are, what are the most common deficiencies and to look for those in the companies that they audit to see whether or not it's as prevalent as what they believe, or whether or not companies are continuing to make the same mistakes despite the fact that the findings are posted and are readily available off the internet.

Now, in looking at these three programs, the importance of them are the following. No. 1, the three programs that we're going to talk about will represent how qualified systems and processes are

Christie (cont.): maintained in a state of compliance. That is the reason why they carry such an important factor to an auditor. You qualify a water system. You qualify a piece of equipment depending on the nature of your product. You qualify storage rooms, whether it be incubators or freezers, whatever, but they are qualified at a point of time. If they pass, that's great.

If they fail a criteria, you do an investigation and you repeat it, but the qualification of equipment, a utility or a system is a single point of time. These programs are designed to help maintain that state of compliance. So, when an auditor comes in and asks to review a qualification of something, they want to see, No. 1, that it passed and met the specific requirements that you have defined, but then they start looking for the programs that maintain them and that is calibration, preventative maintenance and cleaning—three things that greatly impact whatever type of product your company might produce.

The second important factor of these programs is many of these programs today are often contracted out. There is an increased focus of acceptability of the vendors and how quality practices by them are assured. The way that an auditor verifies that you have done that is a vendor audit program. Now, we are not going to talk about vendor auditing during this webinar, but because of the fact that many of these services are contracted out, auditors now will begin to look at what's in place to assure that the vendor is giving you the quality, or performing the quality steps, how the results are handled and how possibly failing results are handled. Again, that's proven to them by seeing that you've conducted a vendor audit and what you audit them against, namely current quality system practices and your company's own quality expectations.

Now, since we've talked about contracted services, the points to remember, but again often overlooked with regards to such services are first, you must remember that results must be reviewed and approved by your own quality unit, so if you contract out calibration services, which is very common today, the expectation is those results are reviewed in some manner by quality. Now, if that quality review is done by the supervisor of the department, that needs to be spelled out in a procedure that defines who is performing the quality function. But the expectation today is that the actual quality unit will review those results at some frequency to assure that specifications are met and more importantly, that any failing result is properly addressed and its impact on product or utilities are evaluated.

The second important thing about contracted services is that if the contracted vendor is following your own procedure, the expectation by the FDA is that you document training of those contracted personnel and that you prove that they have been training on your procedure. Now, one example with regards to this item was one that last year, an FDA auditor walked into a company where the cleaning services were contracted out. Again, a very common practice today and there was nothing about anything that the auditor had reviewed at that point, but while he was walking through, there was a change of shift, and he noticed that the cleaning crew was speaking Spanish.

The first thing he asked when he came back was he asked if No. 1, the people understood English and No. 2, he then asked to see a verification that the procedures that they were following that were developed by the company, they were actually trained on and documented. The results happened to be first of all, half of them did not speak English, which verified that training couldn't be done properly, and No. 2, training was never performed or documented. As a result, there were several 483s that were eventually given to the company.

The third thing to remember about contracted services is the fact that quality or supplier agreements should be in place clearly defining the responsibilities of both parties, meaning who is the main contact for both parties. How are problems handled, as in the next line, critical topics that should be in such agreements are what are the specifications that that vendor should be providing you? If it's a calibration service, what is expected from them in terms of documentation? What is expected of any vendor dealing

Christie (cont.): with failing results? Subcontracting, do you allow a vendor to subcontract the service that you are paying them for and also change control?

I once did an audit for Pfizer when I worked there and we were auditing their service vendors. One of the companies that I had audited for them was sent their analytical balances. Pfizer had no idea that the equipment was then sent out to another company for calibration. When I found out, the first question that came up was how do I know that company. "Did you audit that company?" And the company did. They had it as part of their vendor audit program and so on, but there was nothing notified to Pfizer that the services for which they were getting paid for was then subcontracted out to another company. Again, it ended up generating a revision to their supplier agreement in terms of what the expectation was and whether or not Pfizer was even going to allow that to continue.

Now, we talked about the previous slide, talked about specification. If you go in 21 CFR 820.3, which deals with quality systems, under the word definition, a specification means any requirement with which a product, a process or a service or other activity must conform to. These are the specifications then that need to be defined in the quality agreement because it is part of the requirement of the quality system program.

With that, a little general background on the first section that we're going to now deal with are the regulatory requirements for these three programs. Again, as mentioned, we're not going to get into a lot of detail with these programs, but enough to give you an overall idea in terms of what the specifications are looking for, what their expectations are, and then that is what to take to evaluate your own processes and procedures.

First thing with regards to routine maintenance and cleaning. In 21 CFR 211.67, which deals with equipment cleaning and maintenance, it states in section (a) that equipment and utensils will be cleaned and maintained and sanitized at appropriate intervals. If you are responsible for cleaning procedures, the main word in this requirement that you should be made aware of is the term maintained. The reason for it is when inspectors look at cleaning procedures, they are going to question the fact of how do you maintain a state of cleanliness once an item has been cleaned and how long can it sit before some type of recleaning is expected. That is the main thing that inspectors will look for.

In section (b) of the same requirement, it states that written procedures shall be established and followed. Any regulatory requirement, any guidance document that you may pick up, whether it's by the FDA, the MHRA, Health Canada, all of them require procedures to be the No. 1 thing that you have to have in place. If you don't have a procedure in place, you already have a strike against you when the audit starts.

Then, in section (b3), it requires that a description in sufficient detail of the methods, equipment and materials used to be defined. So, if you are writing a procedure for cleaning or calibration, it's not just enough to say, "Calibrated to these three points," or, "Replaced the motor following the applicable procedure." They expect you to have in there detail that if you or a new employee would go up and read the procedure, that there's enough detail in there that they know what to do and how to do it. A lot of the deficiencies that you will read about, and some that we will highlight as part of this presentation, will actually show you how many times procedures are referenced.

With regards to cleaning, as we started to mention, issues often cited by auditors when they are looking at cleaning procedures are the following. No. 1, does your procedure state how long can a cleaned item remain unused before recleaning is required? I know when I was at Parke-Davis, everything that we cleaned had a tag on it indicating the date cleaned and we had an inspection the one time where an auditor said, "So, what happens if this sits for two weeks? What do you do? Where on this piece of equipment

Christie (cont.): indicates the date by which a degree of recleaning is required?" That time, that was something we got cited for and it is now a common question in other audits that I have witnessed.

The second thing is what degree of recleaning is performed when required. Depending on the nature of your cleaning process, if recleaning is required, do you repeat a portion of it or is the whole process repeated? There is no right or wrong, but whatever you require, it has to be defined and then, it also has to be assured that the operators are following it. Both of them should be included in your applicable cleaning procedure because they are common questions that come up and auditors look for it when they are looking at the status of equipment that they see being held within the company.

With regards to calibration, in 21 CFR 211.68, that talks about automatic, mechanical and electronic equipment, it states in section (a) that if such equipment is used, it shall be routinely calibrated, again, they don't tell you a frequency. It should be inspected or checked according to a written program and that written records of those checks and inspections shall be maintained and documented, so that if a question is asked, you are able to produce the results.

A typical audit question by an inspector with regards to calibration programs is the following. How many calibrations have missed their due date? Calibration programs, for those of you who are responsible for it, you will see in a later slide what the expectations are in terms of documentation, but a good question for an auditor to see a state of compliance is that very question. How many have missed their due dates?

In 21 CFR 820, again, the quality system regulations in their section dealing with inspection measuring and test equipment, it states in section (a) that each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked and maintained and that activities for handling, preservation and storage of equipment shall be documented. Almost identical to the previous slide where we referenced 211.68, but the interesting thing about this requirement is the last sentence, activities for handling, preservation and storage of equipment. This usually goes back, or the area where companies are found deficient, is the storage and handling of the standards. Most calibrations' documents, whether you contract it out or you do it internally will show you all the data expected for the actual calibration of the instrument.

What a lot of companies tend to fail on is procedures and requirements for the handling of the standards themselves. It's especially critical in thinking back again to audits that we had when I was at Parke-Davis, when an auditor would come into the laboratories and look at ultra balances that would give weights within hundredths or thousandths of a gram and they were so sensitive that they would usually be under a covering so that air flows within the room didn't cause the weights to go up and down.

When an auditor would look at that type of equipment, he would look for procedures that said how do you handle the standards for such low weights. If you're familiar with it, standards for ultra balances usually have to be picked up by a tweezer. If you touch them with your hand, the oils of your hand can alter the weight of the standard. Most companies require the wearing of gloves. That is what they are looking for because if you don't maintain the standards, you can't accept the results of the calibration. So, a point well worth remembering.

Also in 820.72, it states in section (b) that calibration procedures shall include specific directions and limits for accuracy and precision and where such limits are not met, there shall be provisions for remedial action and evaluation of any adverse effect on the device. A couple of points worth remembering here. First of all, calibration results or the documentation should not only show what the results were, but it should clearly state what are the acceptable limits or parameters by which that value must meet. That helps determine whether or not you actually are showing the degree of accuracy and precision that has to be met.

Christie (cont.): The other point that is often underlooked is what happens and where is it defined, the procedure that states what your actions are to a calibration result that fails. Keep in mind calibrations generally involve three points of reference and maybe one out of those three points fails, but the expectation is all have to pass. The question to you, then, becomes where in the procedure does it state what your actions are to a failing result and if it's not there, you can be sure that you're going to be issued a deficiency for it.

Now, remedial action might be you can't use the equipment. Remedial action might be a reduction in the frequency or an increase in the frequency of calibrations based on the history of results. Again, it all—they're looking for the detail in terms of what do you do when something doesn't pass. What do you do when during a preventative maintenance, you have to replace an item? What do you in the cleaning program where the cleaning results fail, how is that equipment handled and so on.

The next thing within the quality system regulations, again in terms of calibration, it states in section (b1) that calibration standards shall be traceable to national or international standards. That should be found right on the form used to document results. So, if the services are contracted out or if you perform them in-house, the form that you use to document the actual results obtained should list the national or international standards by which you are following as part of that procedure.

I will tell you, in auditing several companies that do calibration services or even vendor audits that I've done, I am surprised at the number of calibration results given to companies making no reference to the national or international standards that they follow. According to the quality system, it would be a deficiency that you would be cited for. If there are no applicable standards that exist, the manufacturer should establish and maintain an in-house standard and again, procedures that reference how you are going to maintain those items.

In the same quality system regulations in section (b2), it states that equipment identification, calibration date, the person performing the calibration and the next calibration due date be documented. That is a given. The documentation of all results is a given today in terms of the expectations.

The next point is the one that I think companies need to be aware of. The regulation states that these bits of information should be displayed on or near each piece of equipment or readily available to personnel using such equipment. So, if you are doing an internal audit of your practices or when I have done vendor audits and I go up to a piece of equipment that I know requires calibration, I will look for a sticker that shows that that equipment has been given some type of ID number, whatever it may be; that I clearly see the date it was calibrated; its due date; and the initial or signature of the person who performed it. That gives me the ability to simply record that ID number and go back during the audit, ask for the records and that should show me everything I need to verify with regards to that piece of equipment.

The other thing that auditors are looking for and why this point is important is because of the fact that auditors want to make sure that if a person goes up to a piece of equipment that requires calibration, let's say an incubator. You're looking at a sterilizer and the components. You are looking at a temperature sensor within a room. By having the information clearly displayed, an operator knows immediately whether or not that critical piece of instrument or a gauge is within calibration accuracy and it if wasn't, the inspector would not expect to see the operator using that instrument or making or recording the data displayed by that gauge, whatever it might be. That's the reason why they like to see it displayed right on the unit or readily available so that part of the procedure requires the operator to verify that the item is within calibration frequencies.

Christie (cont.): Now, the common expectations with regards to all three programs that we've already talked about in different degrees of detail is one, the establishment of schedules for frequency. Calibration, you have to define the frequencies by how often is it calibrated. Cleaning the same thing. Cleaning programs usually are broken down into a series of activities that are either defined as daily, weekly, monthly or whatever it might be. The auditors expect to see it and they expect those activities to be performed at the frequency defined.

The second thing that you cannot get away from is the establishment of defined procedures and the methods to be used. If you contract out a calibration service and they follow their own procedure, the expectation is that those procedures are reviewed by the quality unit to assure that they meet your quality standards. At a minimum, you should have a copy of that procedure on file so that you can prove to an auditor you know exactly the procedure that is being followed.

Third thing is the documentation of the results. With calibration, again, we're going to talk about it a little bit more detail some of the things that should be documented. We already talked about the information that should be clearly displayed on items that get calibrated, but we're also going to talk about the documentation of cleaning, for example, where samples are taken. What are the limits that you are using? What were the limits that were obtained and whether or not your methods for determining the levels of residuals in a cleaning program are validated. Have those methods to be able to detect limits have been proven to be accurate themselves?

The fourth thing that cannot be overlooked, and realizing that deviations will occur, is the fact that when deviations do occur, that there is an evaluation made on the equipment or the product. One of the probably most common citations you will find is the fact that the level of evaluation did not exist or the level of evaluation was insufficient based on whatever the failing result might have been.

With that, the next topic we're going to talk about are issues dealing with frequencies, limits and the trending of results. All of these items are associated with these three programs to various degrees. In terms of the establishment of frequencies, it's the first thing that should be defined in your procedure. You write a procedure for calibration and calibration especially, or with all three programs, there are different frequencies for different activities. Preventative maintenance has a series of activities that are performed at different intervals. Cleaning the same way. There are activities that are performed daily versus maybe a monthly activity. Calibration, what is the frequency? Is it monthly, quarterly, once a year? After writing the procedure, the frequency is the second-most important thing to make sure that it's defined.

The problem that companies have is when you first write a procedure, you really don't know what is going to be the best frequency because you have no data to evaluate or to trend and therefore, the initial frequencies are often based on a manufacturer's recommendation. You get a new piece of equipment in and you ask the vendor or the manufacturer, "How often do you recommend performing these PMs?" A lot of times, PM frequencies will be in the operator's manual. Calibrations you will usually ask the vendor, "How often do you verify calibrating the critical instrument or a gauge?" Keep in mind the fact that when you talk about calibration, as noted at the bottom of this slide, that vendors don't know specifics such as what is the environment that that particular instrument or gauge is going to be used in. That has a definite impact in terms of the frequency for calibration.

What's the criticality of the information provided? If I make a temperature and humidity sensor used to monitor a clean room, I don't know what the criticality of that information that that gauge is going to give you in terms of how the company is going to use it, but that's a parameter that you have to use in terms of helping to establish and defend what the frequency is.

Christie (cont.): Then, the final thing, the stability of results over time. That's why trending gets to be such an expected practice. I want to see trends of calibration results at these points. I want to see the trending of things that are replaced as part of your preventative maintenance program. I want to see trending of cleaning results. What are the residual levels for various products, various pieces of equipment because the trending of the data is going to tell you over time whether or not those limits that you have established are adequate or whether or not they have to be modified.

Now, when you establish frequencies, it is common that you're going to change those frequencies once data is accumulated. Inspectors like to see that because they verify that the data is routinely being reviewed and evaluated. Somebody is looking at it.

The second thing is frequencies can either be time-based or based on equipment responses such as reduced flow rates, increased pressure differentials, decreased conductivity values. Again, the regulations don't stipulate what data source you have to base a frequency on. They are leaving it up to you, but they expect that those frequencies are based on data that is gathered, evaluated and trended. With regards to preventative maintenance programs, I often think of water systems like an RO system where you look at the frequency of changing filters or you look at decreasing the frequency of calibration because of how stable a piece of equipment might be.

With regards to operation limits, these are the limits that are usually obtained during the operational qualification testing of equipment, cleaning practices over whatever the expected range or the history or the variety of products that you're running. It's important to note that limits established are to be based upon the capability of the equipment or the process or the system and not just a regulatory requirement. What I mean by that is if you establish, let's say, a preventative maintenance program for testing of filters in a clean room and a regulatory limit gives you X amount of particles or X amount of differential pressure, inspectors will usually be concerned when the routine data that you collect is far less than what the limit is, and yet the company will use the regulatory limit as the establishment of let's say action or alert limits. Inspectors want to see limits based on the history and capability of what that system has been demonstrating to you as you collect the data.

Limits for cleaning need to be based on worst-case criteria such as solubility, viscosity, active ingredients, etc. They want to see a scientific rationale for how do you determine a worst-case product for cleaning limits. Rationale as to what constitutes worst-case is expected to be defined. They like to see it defined based on a scientific justification and not just because it was a result that gave you passing values.

When activities such as calibrations are contracted out—we talked about this—it is the company's responsibility to assure that the range of calibration testing is suitable for the equipment usage. Now, with that, if you are calibrating let's say a floor scale that will weigh up to 1,500 kilos, and you contract out the service and the company that comes in only has standards that calibrated up to 1,000. The expectation is that that piece of equipment is clearly defined in terms of the acceptable range of usage. Inspectors will look at equipment that has an enormous range of usage and verify whether or not it's actually calibrated over that entire range. If not, then that's where they expect to see the limits clearly defined. Also with regards to calibration, they should include as-found and as-left values because they are helpful in any potential investigation that you might have to perform as a result of a failing value.

Trending of data is expected as it helps determine when results begin to drift from what is considered normal and it is also a responsibility of the quality unit to assure that results are within limits and performed as required—a basic requirement of a quality system expectation.

Christie (cont.): Then, the other thing about trending that really impacts, let's say cleaning programs is that trending helps to define the impact of seasonal changes and acceptability of the limits that currently might be used as part of your procedure.

Points to remember. The FDA will focus on any of these activities that are contracted out and they will look for the following. Approval of the procedures used by the contracted service and training of personnel when using your own corporate ones. They are going to be looking for the documentation of results and a verification or statement that says the results met the specifications where applicable. You should not have to look at a calibration piece of paper and try to figure out whether or not all the values met spec. Yes, you want to see it, but there should be a statement by the contracted service that clearly defines that they have made a review and verify the results meet the specifications agreed upon.

In terms of calibration practices, a verification, as we mentioned earlier, that there is reference to the calibrated standard used for the test equipment. They also should be verified to be within date and adequately challenged at different test points. Again, that could be found in their own procedures.

Now, the final section of this webinar are the common deficiencies found with regards to these programs. With regards to preventative maintenance, things that are often found, frequencies and procedures are not defined or followed as specified; that the preventative maintenance items are not performed on the due dates established and I'm going to mention a recent 483 here, depending on how much time we have left. Another common deficiency is that there is no or insufficient evaluation of impact on product if failures were encountered or if something had to be replaced as part of that preventative maintenance procedure.

Auditors will look at the trending of causes for deviations or out-of-specification results that list equipment as the reason. This in turn will cause an increased review of preventative maintenance programs, their frequency and adequacy as the potential reason for why. So, there are ways by which auditors tend to come back to these programs and since all auditors like to find out things that failed and look for causes, whenever they start seeing a cause of a failure to be equipment, then the question of preventative maintenance, maybe calibration, get to be more of an issue.

In November of 2011, the following 483 was given to a major pharmaceutical company that said, "Routine preventative maintenance activities were not performed at their scheduled intervals. As of 11/11/11, there were 107 required PM activities for GMP equipment past their due dates. To be considered past due, the event had to be X amount of days beyond their scheduled due date. There was no evidence that the Quality Unit took action on any of these overdue PM activities."

A point worth remembering that I have highlighted. A lot of companies—and I will tell you, we did the same at Parke-Davis—had what we called a grace period for a PM activity or especially a calibration activity. We would define the frequency calibration monthly, grace period, one week. So we could go a week beyond the due date and still consider the equipment to be usable. We had it defined in our procedures, Quality agreed to it. We had an inspection and the auditor said, "I see you have what you people call a grace period."

What he did not agree to was the fact that the grace period did not change based on the frequency of the calibration, meaning if I have an instrument that requires calibration monthly, my grace period should be shorter than a grace period allowed for an instrument that got calibrated every six months or every year and it was a point well made. In this case, they are allowing grace periods to be incorporated, but as mentioned earlier, they look for how many have been missed and then, the other thing with grace periods, if you use them, make sure that they are different based on the frequencies of the calibration.

In three recent FDA inspections of last year of companies that I am currently working with, each making

Christie (cont.): sterile products, each of them was cited for the quality unit not reviewing adherence to schedules and results, especially those involving changes to equipment or utilities. They were cited for the quality unit not reviewing the results of PM activities and calibration activities.

Now, those companies are now in the process of trying to get a handle in terms of how best to handle the volume of PM activities and calibrations performed and how often quality is going to be making a review of that information. It's one thing to be cited for an observation like this. It's another one to come up with a resolution that you can maintain and defend.

Issues covering preventative maintenance was cited as the 10th most common GMP deficiency by the FDA between 2011 and March of 2012. The section often cited of the regulations was 211.67, which I have defined here in terms of what the expectations were.

In another 483 issued to a human pharmaceutical manufacturer, they were cited for the fact that, "The SOP for preventative maintenance was incomplete in that it does not describe the steps or procedures that technicians are to follow…in addition there was no training records available for the technicians responsible for the preventative maintenance program." So, now training is a critical requirement, as we talked about training of contracted services, training of your own people to show that they know what they have to do.

Deficiencies associated with calibration would include no documentation of as-found and as-left values, no statement as to whether or not the results met the specifications. Specifications allowed were not defined on the documented results. No verification of calibration results for the test standards that were used and what were they. No evaluation of product impact or system impact when failures were encountered. Most of the calibrations that I can remember that failed for us usually failed at one of the three points tested. Then, based on that, we would have to look at its impact in terms of did the failing calibration affect the range by which that instrument or gauge was routinely used for, or did it fail at the test point higher or lower than what the normal usage range was.

Ninth most common GMP deficiency cited by the FDA last year dealt with 211.68 that talked about automatic, mechanical and electronic equipment that, again, routine calibrations is the 9th most common one of all the companies inspected.

Deficiencies associated with cleaning. Normally that the procedures detailing the methods, frequencies or solutions to be used were not defined and again, detailing the methods. If part of your cleaning procedure is swab samples, the expectation is inspectors like to see how is the swab sample taken. Is it vertical? Is it horizontal? How large of an area is swabbed? Where is the swab taken? That's the level of details that are usually cited as being deficient in terms of the procedure.

No verification of dilution concentrations where applicable. If a cleaning program requires an operator to make a dilution of a concentrate cleaning, how is that documented? How is it verified? No rotation of disinfectants. Inspectors expect that you have more than one disinfectant that is being used on a rotational basis.

The final thing, which I think is a good point worth noting, a deficiency that says there is no defined increase found in the procedure in the cleaning requirements to cover situations where an area's cleanliness is compromised, meaning if I have a clean room, a clean area, and I have my procedures defined for routine cleaning, what happens when that clean area now something fails to the air-handling units and the cleanliness is now compromised, especially if it's a sterile suite? The expectation is the level of cleaning to bring it back up to normal should be more than what's defined as a routine basis. They want to see that in the procedure. What is the additional cleaning required?

Christie (cont.): The equipment cleaning was the 7th most common GMP deficiency and again, the deficiency covered responsibilities for cleaning, how equipment is supposed to be maintained and again, procedures that address those issues.

In July, another 483 was issued saying the "…the cleaning validation protocol for the tablet press, the specific rational for selecting the most difficult to clean or dry was not included in the protocol or the final report. Eight swab locations were identified with no rational provided." So, again, you have it in a procedure, but they want to see the reasons for it and how did you come up with that requirement.

All right. That's the presentation. I'll take questions now. I know one came in. I'm sorry I couldn't answer it sooner, but when this ends, if any of you have any questions or concerns that you want to ask after everyone hangs up, that is my email address. I am very good at getting back to you with an answer and be more than happy to help you with it.

With that, I'll take the first question. It says, "Please elaborate on the extent to which calibration results need to be trended. Every piece of equipment or individual calibration values, etc." What I would probably recommend would be the following. No. 1, make your trending of results equipment-specific because an auditor who is really performing an in-depth audit will ask—and a question I frequently got was, "I want to see the calibration for sterilizer no. 2." They are very specific in terms of pieces of equipment that they want to look at.

So, make the trending equipment-specific and then, make the trending instrument-specific, meaning a sterilizer has the following critical instruments: temperature-pressure gauges, vacuum gauges, let's say gauges that measure gas concentrations, whatever they might be. All of that data, because each instrument should have its own ID number, all of that stuff should be able to be called up individually at any point of time and you should be able to give me data that says, "I want to see the stability of that temperature gauge on that sterilizer." By number, you should be able to quickly pull it up and show me the results of every calibration that's been performed. The trending of the data could be what percent from the reference point did it vary. Is it a percentage? Is it tenths of a degree, whatever it might be. You can custom make your programs to give you the level of information that you want, but I would definitely trend it by equipment and gauge or instrument. Hopefully that answers your question.

Another one that came in. Can a contract with the calibration vendor replace the need for a quality agreement if the contract contains all of the required elements? Yes. Your contract with your calibration vendor can serve as your quality agreement as long as you highlight the things that we talked about in terms of responsibilities, topics of subcontracting, handling of deviations, the nature of the documentation and so on. Good question and yes, you can use that contract.

Another question. When establishing a PM frequency grace period, is evidence on how that grace period was determined required? That's an excellent question. To be honest with you, I would probably say if you are going to establish grace periods, I would probably look at what your calibration results have been, the trending of the data for whatever instruments or lab instruments or gauges you are calibrating. I would look at trending the results, see what the stability is, have you had any failures, etc., and then based on that, I would also look at what's your history of missing calibration due dates. To an auditor, that helps them determine whether or not you have sufficient manpower to do what's required. Once you get an idea of the stability of an instrument or a gauge and you have an idea of how many failures you might have had or how many calibrations you missed, I would use that as the justification for how you came up with the grace period.

Christie (cont.): Keep in mind there is no regulation that states what grace periods can or cannot be. An auditor will simply look at what you defined in the procedure and as an example in going back to that 483, they will then verify that you are adhering to what your procedure was. The deficiency was the company had it defined, the number was significant. It was beyond a grace period and the fact that they weren't adhering to their own schedule. Those are the critical questions that I would look at when you establish a grace period, but again the big thing, make sure that you don't have one grace period for all calibration frequencies. The more frequent an item is calibrated, the shorter the grace period would be.

Questions have been excellent so far. Anything else?

Operator: Thank you. Ladies and gentlemen, now is your opportunity to have your questions answered by our presenter. Please remember this portion of the conference is also being recorded, and please limit yourself to one question at a time. To ask a question, please press *1on your telephone keypad. I will announce you by the city from which you are calling. Your name and company will remain anonymous. You may hear a few seconds of silence as we bring you onto the line. You will then be live and will be able to ask your question. You may also submit questions by email to questions@fdanews.com or use the Q&A panel within WebEx.

Christie: Another question came in on the chat line. It said, "What documentation is required for reference-only instruments?" That's interesting that you brought that up. One of the items that an inspector had before I left Parke-Davis, we had a validation that said For Reference Only. We gathered some data and the inspector said, "If you are gathering any information, I expect you to do something with it." Basically he didn't cite us with it, but he said if you are gathering information, I expect you to use to help establish a limit or help refine a procedures, whatever it might be.

A reference-only instrument, I'm assuming the reason for the question is that it does not get calibrated. A lot of companies will not spend the time and money to calibrate a gauge or an instrument that is only for reference. What I would probably recommend would be you have information on that instrument from the vendor. Anything that you buy, you have a data sheet that describes what it does, what its range is, whatever it might be. I would maintain that as part of your documentation, but I would clearly define in the procedure dealing with, let's say, calibration, how instruments that are listed as reference-only will not be calibrated, or will be calibrated, let's say, once a year. But define it in a procedure, again, because the regulations don't specify anything. The auditors just want to see what's your procedure and whether or not you are adhering to it. That's the big thing to keep in mind.

Another question. What are the components of an in-house calibration if there are no established standards or you cannot trace it back to NIST? That is a good question and I'm going to be very honest with you. I can't give you an answer in terms of what you would need to do if there are no standards by which you can trace it back to somebody. I'm going to be very honest. I don't know enough about what companies are doing when they don't have those standards and probably the best thing to do would be I would contact the company that makes that type of gauge or instrument and try to get some input to show that you've done due diligence in trying to establish and give you parameters for what you're trying to accomplish.

Another question. Can you clarify what would be acceptable justification for having instruments labeled For Reference Only and not subject to routine calibration? Good question. One of the first things I think of when I was at Parke-Davis would be gauges that we would have, let's say on incoming water supply. We would have a gauge just for reference only for pressures values. We would have it—and they would be labeled and that's a good point with some of these questions. Any time you have calibration not required or for reference only, make sure that those things are clearly defined in the field with a type of sticker because not all instruments require it.

Christie (cont.): One of the guidelines that I would tell clients is a good starting point is if a gauge or an instrument gives you a value that is not part of your required documentation or does not impact the results used to make a judgment on a pass or fail result, you can use that basis as the reason for labeling something For Reference Only. Anything, any gauge, any instrument, whatever it might be that gives you a value that is part of a specification for operational limits, gives you weights or results that are part of a final test result parameter, that is automatically critical, requires calibration. If it has no impact on the results used to make a decision, then that would probably be a good starting basis for determining a label such as For Reference Only.

Excellent questions and hopefully I'm answering these to your satisfaction. Like I said, as far as calibration, I really don't know the best way other than maybe contact the vendor to get an idea of the best approach to it.

Operator: Thank you. We currently have no callers in the queue, so if you have a question, please press *1 on your telephone keypad now and you can have your question answered immediately.

[Operator repeats instructions for submitting questions.]

Operator: We are currently holding for questions. There are no further questions at this time. Do you have any closing comments before we wrap up?

Christie: One other question came in and I'll answer it. It says, "In your experience, what is the best way to handle PMs that have missed the grace period?" Personally, I would probably do is just acknowledge the fact that the grace period has been missed. It's going to be a activity that you need to trend to evaluate manpower needs, whether or not you have sufficient people, but the first thing to do is just acknowledge the fact and then depending on what the PM is, your procedures should define if that grace period is missed, what happens. We talked about that earlier. Common practices are, whether it's a PM or a calibration, if it is missed and we're assuming it goes beyond your grace period, that that piece of equipment, that instrument is taken out of service and it is not [sic] clearly labeled Out of Service and noted that it will be returned after the PM or the calibration is performed.

Keep in mind that to an inspector, once a due date is missed, the acceptability of the values, even though they still might be within spec are now questionable. That is a point that you cannot argue with an inspector. So, that would be the best way that I think of addressing missed PMs. Define in the procedure what do you now do assuming that it goes beyond that grace period.

A practice I've seen at one company was if it exceeded its initial grace period, that they would give it another grace period extension provided that it was reviewed and approved and documented by the quality unit. The quality unit then would look at what was the nature of what was missed; what was the history of it and so on and so forth. But again, put it into a procedure and think of the best way by which you can handle it.

Operator: Thank you very much. On behalf of FDAnews, I would like to thank our speaker and you. Just as a reminder, if you'd like a recording of this session, you can order the CD and transcript package from FDAnews by visiting our website or contacting customer service. This now concludes today's webinar. To end this call, simply hang up your phone and close your browser. Thank you.