Feature Article: 2005 MARSQA Monitor Article Winner

21 CFR Part 11 Compliance Responsibilities of Vendors and Customers

--By Sourav (Neil) Banerjee

After years of industry experience with 21 CFR Part 11, many vendors have come forward with systems that promise to make compliance with the regulation easy for customers. Yet, the experience with many systems has been difficult for all, and continues to be so. It is imperative that customers correctly understand how to plan, select, configure, implement, validate, and use Part 11 compliant systems. It is equally important that vendors understand what is needed for a compliant system in order to design, develop, deliver, and support such systems. This article attempts to illuminate these issues from a Quality Assurance viewpoint, for the most common type of Part 11-compliant systems used today - non-biometric closed systems. (See side bar on next page for definitions).

The most important principle is that both the customer and the vendor share responsibilities as well as risks in understanding the regulations. The diagram below illustrates how the different aspects of 21 CFR part 11 work together to allow electronic records and signatures to be used with the same confidence for legal purposes as paper records and signatures. Note that making a system compliant with Electronic Records requirements is a prerequisite to making it compliant with Electronic Signature requirements, since the electronic signature is itself an electronic record, and only has value when properly applied to other secure electronic records.

Some aspects of compliance are strictly “out of the box” vendor issues, shown in light blue. Others can only be addressed by the customer, shown in dark red below. (How shocking! You mean I can’t just get compliance out of the box?) The trickiest parts are those that may require cooperation between vendor and customer, shown in a shaded blue. Without the right preparation, understanding, and cooperation on both sides, there is almost no hope of implementing a Part 11 Compliant system.

Starting off together

Vendor Selection and Validation

The first issue for the customer is to remember the first requirement of 21 CFR part Sub Part B, Sec.11.10 (a): Validation. To properly validate a system, the customer must start not only from the requirements stage, but also properly qualify the vendor. (continued page 16)
President’s Message
By: Mike Franks

Thoughts from the President...

Greetings. There were a multitude of things I wanted to do on this Sunday afternoon as my deadline for this writing approached, and I did more than a few of them. Watered and weeded...a couple dips in the pool to battle the 95 degree scorching heat and humidity...housekeeping...and another dip in the pool. But all procrastinating aside, I settled on contributing a few thoughts to the revived MARSQA newsletter – which was nowhere on my list of things I wanted to do.

Before I found myself sitting here though, I thought earlier today I could “tap my 15 year old, fresh out of school for the summer son, Evan,” for a little inspiration or content.

“Hey Ev, I want to write an article for a newsletter and you may be able to help me”. I posed a question, “What does qualify mean to you”? “Uhhg”, he replied. “Uhhg? How do you spell that?” I followed. He offered a more drawn “Uhhhhhh”. “Hmmm, can you tell me the derivation of the word uhhg? Its origin? Can you use it in a sentence?” I queried in succession to each of his responses, all of which were – you may have guessed it – a series of “Uhhgs”.

Okay, it may have been the wrong time, or place, or both, to look for my inspiration so I’m back to Plan A. I am quite certain that this is the right time and place to let you know that a terrific group of people that make up the MARSQA Board of Directors and Committees have been making the time amid their busy schedules this year to keep things going. And not just the status quo either. New initiatives such as awarding two ($2,000) scholarships to MARSQA members to attend the 2008 SQA Annual Meeting and monthly teleconferences of the Board of Directors, have been implemented in addition to reviving this Newsletter, review and revision of the MARSQA guidelines, and the list goes on. In addition to this, the work to plan and produce excellent membership meetings, training courses, and maintaining the MARSQA website continues. And the best of this, the 15th year since MARSQA’s inception, is still to come. Namely, the fall membership meeting which will include special festivities that will surely make it one of the more memorable meetings.

I am very proud of all of the Board and Committee accomplishments thus far in 2008 and will take this opportunity to offer my sincere thanks to each and every one of you who have taken the time to participate, whether as an elected member of the Board, an occasional presenter at a membership meeting or training course, or as a member of a MARSQA Committee. I would also like to thank your employers who recognize the benefits of your participation.

Contributing your time and skills is a great way to develop yourselves and others professionally and ensure the continued existence of resources such as the MARSQA website as, among other things, a way for your employers to locate that next star performer in their cadre of professionals. And did I mention the gratification and fun we have as individual volunteers? Yes, seeing that successful meeting you have helped to plan or otherwise participated in, experiencing an attendee’s gratitude for the training you’ve provided, and working with other volunteers along the way is both gratifying and fun. Lasting friendships and professional relationships are established.

We cannot rely on the same individuals and their employers continually as the resources to accomplish the work of this organization.

We need new members, ideas and contributors.

MARSQA is continuing to improve its services to the members at large and the employers who sponsor them. Stagnation is not part of the equation. We must change to improve. We cannot rely on the same individuals and their employers continually as the resources to accomplish the work of this organization. We need new members, ideas and contributors. So last but not least, what I want to do is to encourage current members to accept the challenge of rising to another level by serving on a committee, as a committee chairperson or an elected official of MARSQA. Your opportunity will soon come to get on the slate of nominees for elected service in 2007. I urge you to consider running for an elected position.

Best wishes for a happy, healthy and productive summer!

Mike Franks
President, 2006
2006 MARSQA Board and Committee Chairs

Officers
President: Michael Franks
Vice President: Nicki Iacono
Past President: Jane Nelson
Treasurer: Janet Emeigh
Secretary: Kimberly Garnett
Directors: Steve Junker
          Nancy Gongliweski
          Mariarose Maria
          Lynda Olsen

Committee Chairs
Communications: Lynann Porter
CVC: Nancy Gongliweski
Education: Joanne Jackson
Historical: Fran Jannone
Membership: Jane Nelson
Nominating: Fran Jannone

MARSQA Mission Statement

It is the mission of MARSQA to:

- Continually strive to advance the research quality assurance professions by providing the resources, programs, and training necessary for the professional development and recognition of its membership.

- Serve as a forum for the open discussion of the theoretical, practical, and ethical applications of the quality assurance profession.

- Foster a partnership between the quality assurance profession and the regulatory agencies that results in the attainment of mutually beneficial compliance.
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Report submitted by: Janet L. Emeigh
MARSQA Treasurer
Membership Committee Update

The membership drive for 2008 is on. The goal is to make this as painless as possible for all involved. We kindly ask that all registrations be done via the web site—even if sending a check. Just go to www.marsqa.org, click on "join" and fill in the information fields. Indicate whether or not you wish to appear in the directory. If paying by check, indicate in the check box and then you are done! If paying by credit card, you will proceed to the checkout. This area will prompt you for credit card information. When you submit the information, please only click on the button once.

We ask that this be done by the individuals for a couple of reasons. The first reason being the elimination of the middle man. The forms and checks go to the treasurer, then to the membership committee. This can cause delays, confusion in membership status and is a burden for a small committee to input and review. This will also lessen mistakes due to deciphering handwriting. We have a great website that we want to utilize to its fullest potential.

Remember: For those of you paying by company check, it is imperative that the individuals for the dues payment be specified with the check. If the individuals cannot be identified in a reasonable amount of time (and effort!), it will be necessary to return the check to the respective company.

Please note: Please review and submit any changes to your personal information on the invoice or on the Members-Only section of the website. All members will be included on the Online Membership Directory unless you specify otherwise when registering.

Benefits of MARSQA Membership:

Here are the benefits of being a MARSQA member:

- Attend training courses and membership meetings at a reduced rate.
- The ability to meet and discuss relevant topics with other QA professionals at MARSQA meetings or courses.
- Access to membership directory.
- The MARSQA Newsletter (published 3 times per year).
- Access to the Members only section of the Website.
- Free resume posting on the website.
- No additional charge for paying online by credit card.
Nominations Committee Announcement:

2007 Open Elections

MARSQA is seeking members to run for the following elected offices of:

   Vice President
   Treasurer
   Director (two positions)

Service in these elected offices will commence in 2007. The Nominating Committee, Fran Jannone (Chairperson) and Kate Fetzer will be contacting potential candidates and developing this year’s approved ballot. If you are interested in becoming a candidate for one of the open positions or if there is someone you would like to nominate, please contact:

   Fran  (jannonef@Princeton.Huntingdon.com  732-873-2550 x6021
   or
   Kate Fetzer – fetzerk@Princeton.Huntingdon.com (email only)

Visit www.marsqa.org for upcoming details or a description of each of the available open positions. This is an excellent opportunity to gain valuable experience as well as contribute to the QA profession.

If you are interested in volunteering for the nominations committee please feel free to contact our committee members Fran, Kate or myself.

Thanks for your continued participation

   Mike Franks
   QAResource@aol.com

MARSQA Board of Directors

If you think you have an interest in running for an Office this year, please check the MARSQA website at www.marsqa.org under the Board of Directors tab and e-mail any of the Board members to find out what's involved. If interested, we will gladly keep your name in mind for this November’s ballot. You don’t need to have extensive experience or to have been a long time member of MARSQA, just a true desire to serve MARSQA and maybe to bring some fresh ideas to the Society.
MARSQA Turns 15!

MARSQA is celebrating its 15th anniversary this year. The Board of Directors and Program Committee are currently working on plans for a special celebration that will occur at our next membership meeting in late fall (October or November). Please watch your email and the MARSQA website for details as they become available. In order to participate in this celebration, you must be a MARSQA member for 2006. Happy Anniversary MARSQA!!!

Computer Validation Committee

As a result of the requests of current membership, MARSQA's Computer Validation Committee (CVC) will undergo a slight shift in format and focus. At a recent meeting, membership indicated the major benefits from CVC were the roundtable discussions about current agency expectation, recent regulatory experiences and specific member issues and suggestions. It has become evident that we may need to return to this type of format to revitalize the group and the discussions that had made this Committee such a success in earlier years. There were also some suggestions for improvement and criterion for going forward. Some points were as follows:

For convenience and due to members scheduling difficulties, these meetings/discussions may take place as teleconferences as well as face to face meetings. There should also be a regular schedule for meetings (i.e. once every quarter, alternating between face to face meetings and teleconferences)

Computer Validation Training may be provided to MARSQA by this group at a later date, but would not be the focus of this group in the near future.

The ongoing benefit to general MARSQA membership from CVC is in the important information and knowledge exchange obtained from the discussion of current issues, inspection experiences, etc.

Membership in the CVC allows each of its members to be part of these valuable discussions and use the forum as a way to workout issues that they may be experiencing. In addition, the knowledge and experience of all the members add up to much more than each of us has on our own. If you would like to be part of the CVC, please contact Nancy Gonglewski at 610-787-3452 or nancy.j.gonglewski@gsk.com.
Communications Committee:

Welcome Readers! I hope you are enjoying this revived volume of the MARSQA Monitor. As the new Communications Committee Chair, I must say that I was not particularly aware of just how much work was involved in ensuring a good, quality newsletter. This is not a one person job. Many hours and days were spent behind the scenes in preparation for this very release alone. We are in need of volunteers to ensure future issues of the MARSQA Monitor continue to bring you the latest MARSQA information and articles. Our biggest need involves individuals who can proof the newsletter for spelling, grammatical and styling improvements. If you are able to spend just a few hours a year to fulfill this need, or if you wish to submit ideas, suggestions, article submissions or volunteer, please contact me (Lynn Porter) via email at communications@marsqa.org.

Historical Committee:

Currently, this committee is responsible for maintaining MARSQA’s records, pictures, etc. It might be fun with our 15th anniversary coming up next year to have the committee put together some special historical presentation for the Chapter. If interested, please contact Fran Jannone at Jannonef@princeton.huntingdon.com.

MARSQA Newsletter Article Submission and Contest

- All article submissions to the newsletter will receive a jump drive memory stick (or other prize valued at approximately $30)
- All article submissions will be entered into the newsletter yearly article contest
- Articles will be judged by an independent panel
- The author of the best article submitted will receive an IPod
- The runner-up will receive an I River / I Tunes (or other similar prize)

Enter your Article this Fall

Calling All MARSQA Monitor Contributors!!

The next newsletter is scheduled for:

October / November

Deadline for all submissions is

22 September 2006

Mailing Targeted for the Week of

November 6th
Webmaster’s Corner

MARSQA Members:

Did you know that one of the benefits of being a MARSQA member is free access to the GXP Forum? The forum is comprised of multiple bulletin boards that have been designed specifically for the Quality Assurance professional in the pharmaceutical industry. Inside, you will find a variety of forums where members discuss a variety of quality assurance issues such as:

- Computer System Validation
- Health Authority Inspections (FDA, EPA, MHRA, TGA, etc.)
- Regulatory Affairs
- Warning Letters

This is just a small sample of what is currently available and alternate forums can be added upon request.

In addition, you will find chapter-specific forums where members discuss plans for membership meetings, training workshops, and other issues that impact the individual chapters. Currently, these chapter-specific forums are open to all GXP Forum users, however, in the future, access to these forums will be restricted to members of each respective chapter.

More information on the GXP Forum can be found at: http://www.gxpforum.org/.

Only registered users have the ability to post messages to the boards, but registration is very quick, and is FREE! To register, please visit: http://gxpforum.org/eye.

As always, if you have any suggestions for other features you wish to see added to the MARSQA website, please drop a note to support@marsqa.org.

-From the Webmaster, www.marsqa.org

Program Committee:

This committee is responsible for the 3 wonderful membership meetings that are put together throughout each year. Committee members recruit speakers and arrange the venues and menus for the meetings. They staff the registration table at each meeting, provide the speaker gifts, run the business card bingo, collect the meeting surveys and distribute the member gifts for completing the surveys. They collate the responses from the surveys to get ideas for future meeting topics and identify members who have indicated an interest in volunteering and send their information on to the appropriate committee chairs. If interested, please contact Jane Pasquito at Jane.Pasquito@spcorp.com.
Education Committee Happenings

The Education Committee presented the GLP fundamentals course to a sold out crowd on June 28 and 29, 2006 in Lahaska. The next scheduled course is the **Analytical Course for QA Professionals** and is scheduled in Lahaska on September 7, 2006. This one-day, interactive workshop is offered for Quality Assurance professionals with little or no experience in chemistry, as well as to provide auditing insight for those with analytical experience.

Topics covered include:

- analytical chemistry
- mass spectrometry
- regression analysis
- pharmacokinetics
- method validation
- auditing strategies for analytical studies

Registration is now open on the MARSQA website. Please check the MARSQA website for future MARSQA educational opportunities.

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2006 SQA Fall Training

25 - 29 September 2006

Join the SQA Education Committee for five days of training dedicated to the advancement of the Quality Assurance Professional and others working in GCP, GLP and GMP environments! Courses are being held on the following topics:

- Basic Good Laboratory Practice;
- Advanced Good Laboratory Practice;
- Good Clinical Practice;
- Basic Computer Validation;
- Advanced Computer Validation;
- BioAnalytical topics;
- Medical Device studies;
- Study Director training;
- and Soft Skills training!

The training will be held 25 - 29 September 2006 at the Hilton Boston Logan Airport in Boston, Massachusetts. For more information on courses and registration, visit the SQA website at [www.sqa.org](http://www.sqa.org)!
Auditing for Impact in GLP

Part 1: Good Advice

Tony Jones, SFBC Taylor, Princeton, New Jersey 08540

This is the first in a series of short articles that will present some ideas on GLP auditing, inspired by recent presentations from the current FDA Associate Director of Nonclinical Laboratory Compliance, Mr. Stan Woollen and his immediate predecessor, Dr. James McCormack. Mr. Woollen gave the following advice on how to raise expectations of the QA professional in his presentation at the SQA 2006 Meeting [1]:

1. Apply 'commonsense compliance':
   - Understand the intent of GLP, read the regulations and the preambles
   - Avoid 'senseless nitpicking'
2. Audit for impact:
   - Link compliance issues to their outcomes
   - Communicate findings in terms of impact, not merely compliance with the GLP rule
3. Generate creative solutions to quality and compliance issues to promote quality research without stifling innovation and improvement.

In summary, referring to the FDA's 'Critical Path' initiative [2], Mr. Woollen said that 'quality research should be on-ramp to the critical path and not a speed bump'. In a separate presentation at a recent MARSQA membership meeting [3], Dr. McCormack conveyed a similar message: QA professional's need to read every GLP preamble together with all the related Guidances and Question-and-Answer documents, in order to have a thorough understanding of GLP. This understanding enables QA to interpret and apply the rule intelligently to observed compliance issues. These articles will firstly explore the idea of 'commonsense compliance' proposed by Mr. Woollen. The starting point for this is to really understand the intent of the GLP regulations. In general, GLP is a system to ensure that drug safety data submitted to the FDA (or other regulatory agencies) are of sufficient quality and integrity to assure product safety, and allow regulators to make sound decisions on the acceptability of the product.

The regulations were adopted because of FDA investigational findings that some safety studies were not carried out in accordance with acceptable practice and contained inaccurate and misleading data [4]. The simplest way to understand the intent of the GLP regulations is to break them down into a small number of fundamental concepts that can be easily assimilated and used in day-to-day auditing [5]. These concepts are:

- Data Accuracy
- Data Completeness
- Data Consistency
- Reconstruction
- Control and Communication
- Training (sufficient and documented)
- Personnel Responsibilities (defined and understood)
- Security

Subsequent articles will review each of these concepts, discussing their historical context and their application in GLP auditing. Then, continuing the theme of 'auditing for impact', further articles will analyze and expand upon Mr. Woollen's comment about 'senseless nitpicking' and present recommendations on how to avoid this in order to provide effective Quality Assurance.

References

June 2006 Membership Meeting

Submitted by Janet Emeigh

If you missed this meeting, you missed a very interactive meeting. First and foremost, MARSQA recognized Jane Pasquito for her hard work and dedication to the society throughout its history, both as an officer of the Board and most recently as chair of the Program Committee (for at least 5 or 6 years). A lot of work and effort goes into planning and coordinating our membership meetings (finding a location, getting speakers with fresh topics, etc.). Many thanks to Jane and her team for a job well done!

Our first speaker, Ken Dammers, got the attendees involved by presenting some questions on each subpart of the GLPs for the audience to answer. There was no one correct answer for many of the questions and the questions inspired some lively debate among the members. Examples of questions that generated the most debate included whether or not dates of facility inspections need to be listed on the QA statement for specific studies and whether or not you need to amend your final study report if you move the study data from the archival location stated in the final report. Even our second speaker, Dr. James McCormack, got involved in the debate (you can take the person out of the FDA, but you can't take the FDA out of the person).

Dr. James McCormack was our second speaker. He provided us with some insight as to what it's like operating from the "other side of the fence" as a Compliance professional for a company subject to FDA inspections. He began his presentation by providing some of the challenges that many CROs and multinational companies face. One such challenge is inspections by other monitoring authorities. Lack of historical perspective, little or no communication with review authorities and confusion of "accreditation" with "compliance monitoring" are just some of the challenges that are faced.

Companies also face challenges from the US regulatory agencies. FDA/EPA environments are increasingly political and volatile; FDA preclearance reviewers may mislead scientific staff on regulatory requirements, and FDA guidance is often vague, inconsistent and/or contradicts regulations.

We need to be able to face these challenges. We (companies) need the monitoring authorities and they need our support. The overall goal is to keep quality and consistency a priority.

Dr. McCormack went on to discuss the OECD principles and in particular multi-site issues. The important message is to adhere to the fundamental GLP principles of "one protocol, one study director, one final report". Additionally, there must be QAU oversight of the entire study and communication between the sites involved is key.
Dr. McCormack ended his presentation by providing some pointers on facing FDA inspections. You should know who is on the inspection team, what are their levels of experience, knowledge of GLPs, education, etc. Are there members from other agencies (participate as part of an Memorandum of Understanding [MOU])? At the opening meeting, you should be prepared to have appropriate facility management present, have handouts of your firm's history and organization and ask about the inspection schedule. You should be prepared to be flexible as the schedule may change depending on what is (or isn't) found.

You should explain your normal hours of operation, but make it easy for the inspection to be completed. It is a good idea to request daily brief opening and closing meetings.

During the inspection, attendant staff should be limited to the minimum required to document what's important and to assist the process. It is not necessary to accompany the investigator everywhere (i.e. the bathroom). Make sure the inspection team has a comfortable environment in which to work. Facility personnel should be prepared with business cards and should be trained to respond appropriately, but they should not appear to be rehearsed. Don't answer questions you don't know and avoid making claims you are not sure are accurate. Avoid "that could never happen" or "that has never happened".

When records are requested, if the record is not immediately available, give an accurate estimate of how much time it will take to retrieve it and stick to it. Don't expect the investigator to forget that they asked for a record, they won't (if the investigator has to ask more than twice for a record your credibility is diminished).

Discussion of issues is welcomed and often helpful to everyone. You should avoid confrontations, but you should not tolerate a team member being harsh, overly demanding or unprofessional. If you encounter this, you should discuss the problem with the district investigator.

For the close-out meeting, facility management should decide who should attend. There should be no surprises. The FDA 483 (if there is one) will be provided for your review. You may request any changes or clarifications before it is signed. Even if you have corrected a problem found during the inspection, the finding will still remain on the 483. It is highly recommended that you respond to all 483s. You should clarify who should receive any post-inspectional correspondence and ask for it to be captured in the EIR. There are procedures for amending 483s (IOM 512.001) if errors are detected after the investigator leaves.

The slides from Dr. McCormack's presentation are available on the MARSQA website in the members only section.
To find out how to apply for a MARSQA Scholarship, log onto www.MARSQA.org

2006 MARSQA Scholarship Winners:

Gina Borgia, GlaxoSmithKline

The message from the SQA co-chairs stated that the forecast called for sunny skies, no humidity and good time for all. There could not have been a more clairvoyant image preparing all the prospective attendees of the 22nd SQA annual meeting, set against the breathtaking backdrop of the Point South Mountain Resort in Phoenix Arizona. Some arrived early for pre-conference training in topics such as, Good Laboratory Practices, Introduction to Computer Validation, GLP and GCP Comparison and GMP Regulations for GLP Auditors. All appeared to be very well attended. There was a complimentary, poolside reception for all those attending the conference which set the resort-like mood for the week.

The location was superb, as those who did not attend every single session at the conference found a plethora of opportunities to spend time in the sun. The title of this conference, "Increasing Awareness of the Quality Assurance profession and Raising Expectations of the Quality Assurance Professional" was poignant as was evident by the opening plenary keynote speaker, James Harris. Mr. Harris gave an energetic speech on the changes effecting society. Explaining that there are currently three generations in the workforce, Mr. Harris went on to explain that the "Boomers" are idealists, the theme of "Generation X" is "Just Do It" and how the Millennium generation are "collaborators." He noted the struggles between the generations and recommended that QA professionals remain ethical to know the people they are working with.

Some of the ensuing sessions over the next few days included, the Bioanalytical Regulatory Update, Validation and SOX, Auditing In Vivo Bioequivalence Studies, Trends in Clinical Quality Assurance, Archiving and several other topics. The two most widely attended sessions were FDA/GLP Regulatory update given by Stan Woolen and FDA/EPA Q&A. Mr. Woolen gave a detailed industry comparison between the years 1995 and 2005. He enlightened all those who attended with the top 7 current 483s issued as well as the top 4 483s issued over the last 20 years. The FDA Q&A session included several questions and answers detailing the agency's expectation of Study Director's involvement in GLP studies. The take home message was GLP Regulations define the roles and responsibilities of the Study Director. They do not define how or where a Study Director should reside. What is most important is that this role and these responsibilities are maintained. In addition, the FDA specifically stated that it is difficult to define exactly what is an adequate practice for each situation, as each situation might differ.

As the recipient of one of the two scholarships offered by the Mid Atlantic Society of Quality Assurance (MARSQA) to attend the Annual SQA Meeting, I'd like to sincerely thank those who offered me the opportunity and the means to attend the conference. I found this trip to be not only informative but also a tremendous chance to network amongst those more experienced in my profession. I firmly believe that the MARSQA organization should continue to offer those in the Quality Assurance profession the opportunity to attend this conference and all QA professionals, who may not be able to otherwise attend, should apply for this career enhancing scholarship.
Courtney Glass, Wyeth

Many thanks to MARSQA for providing me the opportunity to experience and enjoy the annual SQA meeting in warm, sunny Phoenix! The 5-day conference event was both entertaining and enlightening.

The pre-conference GLP Basic Training provided me with a thorough review of the FDA GLP’s. The training was a full-day event, with speakers from industry, university, and FDA backgrounds. Discussions included the scope of the GLP’s, SOP’s, Protocols, Study Conduct, Final Reports, as well as open Question and Answer sessions. I would recommend this training for individuals new to the auditing profession, scientists new to the GLP environment, and individuals seeking a refresher on the GLP’s.

The conference began with a fun-filled poolside reception, where I was able to meet and network with many new faces. This networking continued throughout the entire conference, allowing me to meet and talk with people that I hope to keep in contact throughout my career!

Each day of the conference provided a variety of concurrent sessions to attend with topics tailored to suit a variety of interests. Although I attended many of these sessions, those that were the most interesting to me were the Bioanalytical Regulatory Update by Dr. CT Vishwanathan, and the FDA GLP Regulatory Update by Stan Woollen.

The Bioanalytical Regulatory Update was focused around current issues encountered by the FDA Division of Scientific Investigations. Dr. CT Vishwanathan presented several topics including: Study Conduct/Data Collection, Test Articles in Control Animals, Analytical Site Inspections, Outstanding Issues, Do GLP’s assure Quality Data, and Bioequivalence Issues and Updates. In his presentation, Dr. Vishwanathan recommended that 20% (at random) of the samples obtained from control animals should be assayed in TK studies. He also spoke on the issue of contributing scientist reports, confirming the regulations that “signed and dated reports of each of the individual scientists or other professionals involved in the study” shall be included in the final study report. One additional consideration that was noted in this presentation was the idea of blinding the analyst to QC concentrations by having the QC’s prepared by another analyst not involved in the study. Overall, this was an excellent presentation and update of the current Bioanalytical expectations of the FDA.

The FDA GLP Regulatory Update centered around Stan Woollen’s trip back to Phoenix with a comparison of past and present FDA observations and issues. Topics included current agency-wide inspection and compliance metrics, 483 trending observations, and raising the expectation of the QA professional. The top four FDA 483 trending observations (GLP) are based on: protocol and study conduct, SOP’s, personnel and management, and insufficient QAU. QA professionals were reminded to understand the intent of the regulations and avoid senseless nit-picking, as well as generating creative solutions without stifling innovation and improvement.

Aside from the concurrent sessions, the SQA meeting also provided the opportunity for me to learn about specialty sections, including the GLP Specialty Section in which I plan to participate. This specialty section will provide me with the ability to seek information from a network of professionals with a vast array of experience. Because my background is focused in the GLP laboratory area, with less of a focus on toxicology, I will be able to gain insight as well as provide a slightly different perspective.

The SQA national conference provided plenty of opportunity to learn, be entertained, join new groups, and meet new people. It was a great opportunity of which I am thankful to be afforded. I look forward to seeing familiar faces at future meetings!
In order to properly assess a vendor and their product, the customer must first be able to specify their business and regulatory requirements at a high level. The customer should document their Regulatory risk analysis, as well as which Part 11-related requirements actually apply.

The compatibility of product features with customer needs is only one aspect of choosing a vendor and product. Equally important are the vendor’s practices around the following, which should be included in the overall scope of a vendor audit:

- Vendor’s understanding of 21 CFR Part 11, and assessment of the product with respect to the customer’s Part 11 requirements.
- Training developers on 21 CFR Part 11
- Vendor’s development and testing practices
- Unit, integration, and system testing
- Product certification prior to market release, especially if third party tools are required for implementation
- Test scripts or at least test cases for end user testing that can be customized for a particular implementation.
- Accurate and complete Installation Qualification documentation
- User manuals and user training
- Maintenance and support package for older versions.
- Release notes for any patches/updates with impact analysis and recommended regression testing, in order to maintain a system in a validated state through change control. (The customer’s IT personnel are generally not qualified to do impact analysis of a code change by the vendor’s developers. This is a vendor responsibility!)

The customer, after choosing the right vendor and product, must then negotiate the right kind of support package, finalize...
requirements, determine what are Part 11-related records, and validate according to the customer's own System Development Life Cycle (SDLC). The customer must then implement the system, train users, and maintain the system in a validated state. Regardless of the customer's efforts, it is very difficult to successfully accomplish these goals unless the vendor satisfies the criteria above.

**Useful Definitions**

**Archive.** (IEEE) A lasting collection of computer system data or other records that are in long term storage.

**Audit trail.** (ISO) Data in the form of a logical path linking a sequence of events, used to trace the transactions that have affected the contents of a record.

**Biometrics.** (FDA) A method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.

**Certification.** (ANSI) In computer systems, a technical evaluation, made as part of and in support of the accreditation process, that establishes the extent to which a particular computer system or network design and implementation meet a pre-specified set of requirements.

**Change control.** (FDA) The processes, authorities for, and procedures to be used for all changes that are made to the computerized system and/or the system's data.

**Closed system** (FDA) an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.

**Predicate Rule:** cGMP, GLP, GCP etc.

**Qualification, installation.** (FDA) Establishing confidence that process equipment and ancillary systems are compliant with appropriate codes and approved design intentions, and that manufacturer's recommendations are suitably considered.

**Specification, requirements.** (NIST) A specification that documents the requirements of a system or system component. It typically includes functional requirements, performance requirements, interface requirements, design requirements [attributes and constraints], development [coding] standards, etc.

**System Life cycle.** (FDA) The course of developmental changes through which a system passes from its conception to the termination of its use; e.g., the phases and activities associated with the analysis, acquisition, design, development, test, integration, operation, maintenance, and modification of a system.

**Validation.** (FDA) Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.
Electronic Records (ER): Customer-Only Responsibilities

Documentation
(See 21 CFR Part 11 Subpart B 11.10 (k) for the regulatory reference).

The customer has full responsibility for all documentation, other than the vendor issues mentioned above. The customer must define and document how the system should be used in a secure, regulatory compliant, validated manner. The customer must also define and implement document controls, including:

(1) Control over distribution and access to, and use of documentation for system operation and maintenance.

(2) Revision and change Control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

ER: Vendor-Only Responsibilities

Independent, Secure, Computer-generated, Human Readable and Electronic Audit Trail:

The vendor must build functionality that allows a "secure, computer-generated audit trail to independently record date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Audit trail information must be retained for at least as long as the subject electronic records, and shall be available for agency review and copying."

(Quote from 21 CFR Part 11 SubPart B, 11.10(e)) An audit trail should be comprehensible by an external auditor without any technical knowledge of the system. The audit trail should easily display exactly who made what change to which record at what time and date, and why. The vendor must also provide "ability to generate accurate and complete copies of records in both human readable and electronic form suitable for agency review and copying." (11.10 (c)). The key phrase here is "human readable". The customer must evaluate the vendor's product to ensure compliance in these areas. As noted below, of course, it is up to the customer to define which records fall under Part 11, and therefore must be audit-trailed in this manner.

ER: Vendor-Customer Shared Responsibilities

Many customers and vendors are blind-sided by areas of compliance where both have to cooperate. These include, for ER:

Training:
(21 CFR Part 11 Subpart B 11.10 (i))
The vendor must provide user manuals and training materials for out-of-the-box system functionality. The customer must:
- Define training based on roles
- Provide and document training
- Update training as needed
- Maintain training documentation for inspection if required.

Security and Records Protection:
(Sub Part B sec. 11.10 (c))
The vendor must build technology that allows protection of records to enable accurate and ready retrieval throughout the record retention period (50 years or more in some cases!). Records should be in a secure format that can be easily backed up, recovered, migrated, and archived while preserving the meaning of the information.
The customer must define which records fall under the scope of Part 11, and thereby establish and follow policies and procedures that enforce proper use of the vendor’s technology to provide the requisite protection for in-scope records. Due to technology changes that render data formats and media obsolete over time, there is no industry standard yet on how to meet the 30-year retention requirement, although the best bet may be to archive in an industry standard format, such as XML, that has a high probability of being accessible in the future.

Controlled Access, Authority, and System checks:

(Sub part B 11.10(d), (f), and (g))

The vendor must first build technology that allows controlling of access to system, data, and functionality based on predefined roles, as well as allowing system checks to enforce permitted sequencing of operations. The customer must then define those roles and specify permission levels for different applications, functional areas and data within each application as well as permitted sequence of operations, according to the customer’s business process. The vendor then configures or customizes the system to meet those specifications, if needed. The customer must then validate the system according to those specifications. This type of cooperation is often not anticipated. The results are blame games, delays, cost overruns, and poor quality systems.

Note: At this point, it is important to determine if the system actually needs to satisfy the requirements of electronic signatures as well as electronic records. A systematic, detailed assessment procedure that goes through each section of the regulation, taking into account applicable predicate rules, is highly recommended. Electronic signatures that are applied to records that do not fall under the scope of any predicate rule, will not fall under the scope of 21 CFR Part 11.

Electronic Signatures (ES): Customer-Only Responsibilities

Certification to FDA:
(Sub Part C, 11.100 (c)).

The customer must certify to the FDA that the electronic signatures in their system are intended to be the legally binding equivalent of traditional hand written signatures, and submit this certification to the FDA in paper.

Electronic Signature Policy:
(Sub Part B, 11.10 (j))

The customer must establish and enforce written policies that hold individuals accountable and responsible for actions initiated under their electronic signature, in order to deter record and signature falsification.

ES: Vendor-Only Responsibilities

Signature-Record Linking
(Sub Part B Sec.11.70)

The vendor must design the system to link electronic records to electronic signatures executed on them, such that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means. A signed electronic record cannot be changed without violating the meaning of signature, and making the signature invalid. The vendor’s design should not allow such a change, or at least provide clear indication that the meaning of signature has been violated, and provide audit trail evidence. Unless the customer closely check’s the vendor system’s functionality on this issue before purchase, it is easy to not discover the flaw until the validation stage, resulting in expensive rework and delays.
ES: Customer-Vendor Shared Responsibilities

This is the most difficult part of Part 11 compliance: getting electronic signature functionality to work in areas that both customer and vendor need to cooperate on. The system must be able to verify a signer's identity, have the right signature controls in place, ask for enough signature components, securely link the electronic record to the electronic signature, and provide the correct signature manifestations in human readable format. All of this is absolutely necessary to achieve the original purpose of 21 CFR Part 11 - making electronic signatures as legally binding as paper signatures. If either the vendor or customer fails in their tasks, or they do not understand each other, there is almost no way to achieve compliance.

Verify Identity of Signer
(Sub Part C 11.100 (a) and (b))

The **customer** must define policies to ensure each electronic signature can only be used by one person, and cannot be re-used, or re-assigned to, anyone else.

The **vendor** must build functionality to enforce uniqueness of electronic signature. The application should verify signer's identity by asking for authentication both at logon and at the time of signing.

The **customer** must verify the identity of each individual before customer assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature.

Signature Components and Controls
(Sub Part C, Sec. 11.200)

The **vendor** must design the system to ask each signer to enter two separate signature components at the moment of signing, for at least the first signature in a series of signings during a continuous session. (Subsequent signings during a continuous session will require at least one component)

The **customer** must administer and execute electronic signatures in such a way that only their genuine owners can use them, and falsification of signature will require collaboration of two or more individuals. Vendors have been known to use all kinds of shortcuts here, such as applying "signature components" from the signer's logon event to the electronic record after the signer clicks an "approve" button. This is not an electronic signature! At the moment of signature, if the signer clicks on an "approve" button (or equivalent), a dialog box should appear which asks for the signer to actively enter two separate signature components (e.g. username and password) at that moment. After the signer enters these components and clicks on "OK" (or equivalent), the system should (1) authenticate the user using the signature components, (2) attach the electronic signature to the signed record, (3) Lock down the signed electronic record from any further modification of its contents, and (4) display a message to the signer stating that the electronic record in question has been successfully signed. While these four points are not explicitly stated in the regulation, experience has shown that these features are necessary at a practical level to satisfy this part of the regulation.

**Signature Manifestations**
(Sub part B, sec. 11.50)

The application must be able to display on demand for any signed electronic record in the system, the following:
- Printed names of signatories
- Date and time of signature
- Meaning of signature
- Manifestations must be visible on electronic and printed version of the signed record.

The **vendor** must provide the basic technical capability to meet these requirements, but the **customer** must provide meaning of signature as per their own business process, according to the different business roles that may exist in the organization. This may then require a configura-
tion change from the vendor that the customer must validate. Unless these requirements are met, it is not possible to prove to an auditor that an electronic record has actually been signed electronically, in a manner that is legally binding.

Controls for ID codes/passwords
(Sub part C, Sec.11.300)
The customer must (a) maintain uniqueness of each combined ID code and password, (b) ensure ID code and password issuances are periodically checked, recalled, or revised, (c) follow loss management procedures to electronically de-authorize compromised devices that bear or generate ID code or password info, and control temporary replacements, (d) use transaction safeguards to prevent unauthorized use of password/ID codes, detect and report unauthorized use attempts to security and management, and (e) initial and periodic testing of devices that bear or generate password/ID code information. The vendor must design the system to detect and record unauthorized use attempts, so that the customer can check this information and report accordingly. It is a shock to some customers that they must assume so much of these responsibilities on their own. The vendor can build in safeguards such as checks on ID and password combinations and transaction safeguards, but it is really the customer’s responsibility to ensure that the right policies and safeguards are in place inside their network and organization.

Conclusions
The customer must at a minimum do the following for success:
- Determine which records (if any) actually fall under the scope of 21 CFR Part 11, according to the following criteria from the FDA’s latest guidance document on the scope of 21 CFR Part 11. The following records are in scope:
  ⇒ Records that are required to be main-
tained under predicate rule requirements and that are maintained in electronic format in place of paper format.
  ⇒ Records that are required to be main-
tained under predicate rules, that are maintained in electronic format in addition to paper format, and that are relied on to perform regulated activities.
  ⇒ Records submitted to FDA, under predi-
cate rules (even if such records are not specifically identified in Agency regulations) in electronic format.
  ⇒ Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules.
- Understand 21 CFR Part 11
- Figure out which parts of the regulation apply to their business need, and design high-level requirements accordingly
- Do Regulatory Impact and Risk Analysis
- Use their requirements and risk analysis to select the right vendor and product
- Qualify the vendor
- Negotiate the right contract for functionality, delivery, validation help, support, and other needs.
- Communicate all information needed for customization and configuration to the vendor
- Validate according to the FDA definition, and maintain the system in a validated state through change control.
- Never compromise on needed regulatory compliance.

Vendors who succeed in this market must also understand Part 11, look at general customer needs, design flexibility and configurability into their software, and develop accordingly. The following points greatly increase a vendor’s attractiveness in this market:
Having a well-documented System Development Life Cycle in place, and the documentation to show that the vendor is following it.
- A 21 CFR Part 11 compliance statement, with explanation of how their systems help meet each section of the regulation that is not strictly a customer responsibility.
- Detailed, accurate Installation Qualification documents.
- A Validation package with detailed test scripts that can be modified for individual customer needs, and a complete Trace Matrix.
- Consulting expertise that can help implement and validate systems
- Support Packages that include detailed release notes with information on what sections of the application are impacted by patches or new versions, so that the customer can make accurate decisions about regression testing.

Most importantly, vendors must listen carefully to their customers, especially regulatory experts, to understand the special needs of customers in an FDA-regulated environment.

While vendors can make it much easier for the customer to implement a validated solution, it is the customer's responsibility to fully validate against their own predetermined specifications. Unless both sides have an informed understanding of 21 CFR part 11 compliance, the potential for chaos and failure is high. Success can only come from the right level of understanding and planning at the beginning, for both sides. The rewards are too great to sacrifice. Better patient safety, regulatory compliance, business efficiency, and of course, increased business for all in a growing market.

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**Publication Policy**

The information contained herein are the opinions of the authors but are not necessarily the opinions of MARSQA or the Society of Quality Assurance (SQA).

The editor, MARSQA, and the National SQA are not responsible for any damage.
Call for Volunteers
Are you the type of person who doesn’t like to sit on the sidelines but really likes to be involved? Have you been to a recent membership meeting and thought, why did they present that topic or pick this place, I could have done better? Do you like to take pictures or give your opinion or share your expertise with other folks in the QA field? Have you been disappointed in what MARSQA has done for you lately and felt it could do more?

If you answered yes to any of the above questions, then you should consider volunteering to serve on one of the committees or consider running for an office. For the most part, there is not much of a time commitment required (approximately 1-2 hours/month) and the rewards, contacts and friendships that you gain are well worth the effort.

MARSQA is entirely run with the help of volunteer members. Without volunteers, there would be no MARSQA. If you don’t feel comfortable enough at this point in time to take on a leadership role in a committee or as an officer, there are many behind the scenes ways you can contribute with the various committees. A brief description of each committee and what they do along with the contact information for the chairpersons for those committees are listed on pages 7 and 8. If any of these peaks your interest, please contact the appropriate chairperson for further information. Your help will be welcomed.

Attention Advertisers!
The Mid-Atlantic Region Society of Quality Assurance is pleased to announce that advertisements will be available both in the Monitor, as well as on our website, www.marsqa.org. The fee structure has been discounted to better serve the advertisers, including consultants and corporate sponsor companies. The fee structure will be as follows for the entire year (3 newsletters, website):

- Full page ad: members: $100, non-members: $200
- ½ page ad: members: $50, non-members: $100
- ¼ page ad: members: $25, non-members: $50

The fee structure for placing an advertisement on the website only will be $50 per ad per year. You will have the ability to change your advertisement as necessary throughout the year for both the newsletter and the website. All fees for these new advertising plans will be billed at the beginning of the year.

The fee structure will remain unchanged for placing an advertisement in a single issue of the Monitor only:

- Full page ad: members: $50, non-members: $100
- ½ page ad: members: $25, non-members: $50
- ¼ page ad: members: $15, non-members: $25
- 2" x 3 ½" ad: members: free, non-members: $15

If you are interested in more information or would like to place an advertisement in the next issue of the newsletter or on the website or both, please contact Ms. Lynann Porter at 610-787-3471 or by e-mail at Lynann.M.Porter@gsk.com.
Calling All MARSQA Monitor Contributors!!

The next newsletter is scheduled for:

October/November

Deadline for all submissions is

22 September 2006

Mailing Targeted for the Week of

November 6th

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23RD SQA ANNUAL MEETING  Austin, Texas 29 April - 3 May 2007

Hittin’ the High Note on Quality: Capitalizing on the Benefits of QA throughout an Organization

CALL FOR ABSTRACTS

The Society of Quality Assurance is pleased to invite you to submit an abstract for consideration for the 23rd SQA Annual Meeting, 29 April - 3 May 2007 at the Hilton Austin in Austin, Texas, USA. The theme of the meeting is “Hittin’ the High Note on Quality: Capitalizing on the Benefits of QA throughout an Organization.” The Program Committee will consider all regulatory QA topics for presentation: manufacturing (GMPs), preclinical (GLPs) and clinical (GCPs). Other areas of interest may include animal health, bioanalysis, biotechnology, computer validation, medical devices, scientific archiving, university issues and much more. The abstracts will be reviewed and selected for presentation based on timeliness of topic and applicability to the theme of the meeting. Abstract submission will close on 30 September 2006. Submit abstracts now via www.sqa.org!

ABSTRACT SCHEDULE:

- Abstracts reviewed: 16 October 2006
- Abstracts assigned to sessions/posters: 24 November 2006
- Acceptance notices sent to authors: 1 December 2006
- Session chairs assigned: 8 January 2007
- Meeting grid published: 8 January 2007

Conference Registration will be available December 2006. All presenting authors of abstracts accepted for presentation will be required to register for the Conference and pay the appropriate fees, in accordance with the published fee schedule. For more information on abstract submission, visit www.sqa.org.

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Many thanks to the individuals who donated their time and support for this issue of the MARSQA Monitor!

Special Thanks to Meredith Russo for providing the June Membership Meeting photo’s seen throughout this issue.

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