



“News from the Heartland”
Mid West Society of Quality Assurance Newsletter
June 2008



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Please submit articles for the next newsletter by **August 29, 2008** to editor@mwsqa.org



Presidential Ponderings

Barbara Stephenson, Pfizer, Inc.
President, MWSQA

The MWSQA chapter has continued to stay busy since the issue of our Spring newsletter.

- The audit committee is working on the 2007 audit. Targeted completion date of the audit is July. This will be the first audit conducted since we merged our finances with SQA HQ.
- Completed our first year of our partnership with SQA HQ. We are still working out the bugs but we have integrated our finances and membership registration processes. At the beginning of next year we plan to integrate our website with SQA HQ. We are hoping to obtain a members only access to the MWSQA website at that time.
- Margaret Coyle-Rees from Leifheit & Company Inc., Racine, WI won the \$2000.00 scholarship which was used for expenses incurred to attend the annual SQA meeting in Memphis.
- Completed our first Meet & Greet at annual SQA meeting
- MWSQA presented a poster session at annual SQA meeting.
- Planning committee, consisting of 14 MWSQA members, is advancing the planning of the MWSQA summer meeting sponsored by Covance Inc. in Madison, WI.
- 2008 membership to date is 259

As you can see, the MWSQA BoD and planning committee have been busy.

Our chapter is only as good as those who volunteer to support it. It is no wonder we have such a vibrant, rich chapter. You are the ones that make it happen. I encourage each and every one of you to participate in your chapter.

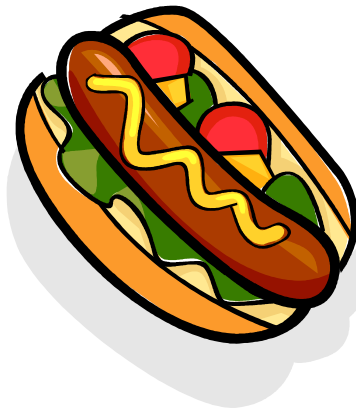
Here are some things you can do:

- Run for a BoD office, there are four people rotated off every year. Contact Andrea Steed now regarding running for an office at the end of this year. It's not too early to make this decision.
- Present at our annual meeting – contact any BoD member or planning committee member
- Sponsor the meeting – See sponsorship procedure on our website or contact Tim Valley
- Volunteer to help at the annual meeting – contact Tim Valley
- Write an article for the MWSQA newsletter

I would like to thank all of the individuals (members and non-members) who participated in the Meet & Greet during the annual SQA meeting in Memphis. I had a great time meeting some members for the first time, meeting some soon to be members and reminiscing with those of us who were members beginning in 1991 (Springborn Life Sciences in Wapakietta, OH, remember Ralph Anderson, Anita Bosau, Lynn Klahm, Connie Marvel, Margery Wirth?). I had forgotten the MWSQA beginnings. While we ate breakfast together I was reminded that the original annual membership fee was \$5 (we were not sure anyone would join at that price), the newsletter was sent out snail mail (the \$5 was to cover the postage), we commonly had \$500 or less in the bank (not enough to cover a bi-annual meeting should it go bust) and the total

membership was around 25. Those were the days! We certainly have come a long way and built a successful chapter. Thank you for your participation and corporate support and thank those of you who attended the MWSQA Meet & Greet. I think we need to place it on the agenda for next year, Tim!

See you in Madison! Great presentations, Mallards baseball, hot dogs and beer and of course all our MWSQA colleagues! Could life get any better?



Hot Dog – MWSQA July meeting in Madison **Hit a Home Run with Quality!**

Tim Valley
Covance Inc.
MWSQA Vice President and Planning Chair

Hello from Madison, Wisconsin!

Well all the snow has melted, and people are out and about again. Neighbors and friends cooped up all winter reacquaint themselves and schedule summer parties. That's the thing about Madison, give the locals sun and mid 50's and everyone is grilling in their backyard and donning shorts and Hawaiian shirts.

Planning for the MWSQA summer meeting is coming along. The summer meeting will be held at the Fluno Center in Madison, Wisconsin and sponsored by Covance Inc. on 29-30 July. The registration flyer is scheduled for distribution soon. Tentatively the meeting will include three training sessions (study director training, application of problem-based learning to GLP training, and computer validation), and an update on the GLP modernization process. Presentation topics include test article characterization, device characterization, computer validation, veterinary biologics, clinical research issues, and trouble shooting anomalous bioanalytical results. Dr. Fred Kirchner, Director of Toxicology Services at Covance Inc. in Madison, Wisconsin will be our keynote speaker and will present on the value senior management places on quality assurance. Included as part of the meeting, we will spend Tuesday evening at the Mallard ball park where we will enjoy a gourmet dinner of beer and hot dogs.

We anticipate a large turnout for the meeting so be sure to register and make your reservation at the Fluno Center (877-77-FLUNO or direct at 608-441-7117) early.



GLP Hot Topic- Contributing Scientist Reports

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GLPs (FDA 21 CFR 58.185(a)(12) and EPA 40 CFR 160.185(a)(12)) require final study reports to contain “The signed and dated reports of each of the individual scientists or other professionals involved in the study.” EPA regulations add, “...including each person who, at the request or direction of the testing facility or sponsor, conducted an analysis or evaluation of data or specimens from the study after data generation was completed.”

While these requirements seem simple, their application can be interpreted in various ways. Historically, contributing scientist signatures were primarily obtained by having in-house pathologists sign the signature page of final reports, or in the case of multi-site studies, a principle investigator would provide a signed report to be appended to the final report. For many years, there were no significant regulatory actions associated with this procedure.

However, a review of recent FDA Form 483 citations and statements made by FDA officials at trade meetings, show a new focus on contributing scientist reports. For example, a Form 483 for a May 2007 inspection:

“The final study report did not include the signed and dated reports of each of the individual scientists or other professionals involved in the study. Specifically, the final report for study XXXX did not attach the signed and dated report for the clinical pathologist interpreting data for the study.”

Previously, in 2005 a Form 483 was issued to another facility. The following was excerpted from the Establishment Inspection Report (EIR):

“Specifically, for study XXXX, the Study Director's final study report did not include reports on interpretation of gross evaluation of uterine horn abrasion results and microscopic examinations. The final study report stated that “Gross evaluation of rabbit uterine horn abrasion results will be reported separately by the Sponsor. Microscopic examinations were done by the Sponsor on selected tissues from perfused animals, and the results of this examination will be reported separately by the Sponsor.”

A warning letter was in May 2006 which states:

“The signed and dated reports of each of the individual scientists or other professionals involved in the study were not included in the final report [21 CFR 58.33, 58.185(a)(12)]” “...The study report did not include the pharmacokinetic data and analysis, did not address why they were missing, and did not identify the scientist or other professionals involved in that portion of the study.”

Clearly, the FDA has placed a renewed focus on this GLP requirement. The interpretation of what constitutes a contributing scientist, in terms of requiring a report and signature, seems to

be expanding to include in-house clinical pathologists, veterinarians and other staff. These scientists may have provided informal input into writing the final report in past, but did not necessarily sign the report.

Indeed, it could be argued that statistical analysis performed by an in-house professional statistician would also require a signed report. This would be in accordance with EPA's "...or evaluation of data or specimens from the study after data generation was completed."

It has been generally accepted that a separate signed report from principle investigators in multi-site studies is required (See OECD Guidance on Multi-site studies). Also, pathologists have typically signed either the final report or a separate section of the final report. The focus on other professionals, such as clinical pathologists is a relatively new development. Additionally, a contract facility issuing a "final report" which does not include portions conducted by the sponsor has drawn citations.

The original intent of the signature requirement was to ensure the accountability of scientists to the results reported. It also serves as a check on changes to a contributing scientist interpretation in the final report, without their knowledge. Certainly, there can be disagreements between a study director and a contributing scientist. However, these disagreements can be resolved either before issuing the contributing scientist report, or by the study director discussing the topic within the overall final report. For example, pathologists have engaged in a peer review process to resolve any differences in interpretation of pathology slides.

In light of this new focus, organizations should review their procedures for writing and signing reports. Any scientist, who provides an analysis or interpretation of the data, may be viewed by the regulators as person who should sign. I recommend the following:

- Study pathologists should always sign
- Portions of a study conducted at another site (Multi-site) should include the generation and signature of a report for activities conducted at that site. This should be included in the final report as an appendix.
- Scientists who provide expertise in writing and/or interpreting a section of the report (i.e. do they draft a section for the study director?) should be evaluated as a potential signatory. Some FDA findings have resulted from discovering a contributing scientist draft report section(s) that was used as a basis for the final report.
- Reporting requirements and signature procedures should be defined in a Standard Operating Procedure.

Each organization must review their own processes and management must make reasonable judgments of how far to go with reports and signatures. Regulatory risk must be balanced by a reasonable approach that can be justified and defended to regulators. Mechanisms for capturing the "signed and dated reports" of individual scientists may vary. One option is to capture all applicable internal scientist signatures on a single signature page within the final report. Alternately, it may be preferable to have a signed contributing scientist report as a section or appendix within the final report.



QCA: More than Just a Pretty Acronym

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Many of you have probably found yourself reviewing a report or article in which the term “quantitative coronary angiography” was given a brief mention. Some of you may be perfectly familiar with this term, while others are left to ponder, what in the world is that?

At a basic level, angiography is the X-ray study of blood vessels.

The procedure takes place in a fluoroscopy suite and requires the injection of contrast medium into vessels to make them visible under X-ray. To accomplish this, an arterial puncture must be completed. A technician will clean and prepare the puncture site, usually in the groin or neck, and create a small incision in the skin to help with the insertion of a needle into the artery. Through the needle, a long guide wire is advanced and directed by fluoroscopy (moving X-ray) to the location where angiography is to take place. Once the area of interest is visualized, a catheter is advanced into place for the injection of contrast medium by hand or an automatic injector (depending on the type of angiography that needs to be completed), and the guide wire is removed. There are several types of angiography that can be done, including coronary, pulmonary, cerebral, renal, and celiac and mesenteric. Fluoroscopic pictures are recorded in rapid sequence during the injection, producing an angiogram. From angiograms, the angiographic core laboratory can begin to work its magic.

An extensively trained analyst loads the angiogram onto a computer with highly specialized software for quantitative coronary angiography (QCA). The computer program enables the analyst to evaluate a number of different parameters, depending on the needs of the sponsor or investigator. To begin, the analyst must review the angiogram to search for the ideal image to evaluate. This begins by first selecting the appropriate image run (a short “movie” of the injection) and calibrating it based on the diameter of the catheter tip, which should be readily visible within the field of view on the screen. The analyst then examines the image run frame by frame to capture the vessel at exactly the ideal point for analysis. Typically, a large part of the process involves manual tracing of the contours of a vessel before and after an intervention. From the tracing, the analyst is able to obtain a variety of measurements such as reference vessel diameter, minimum lumen diameter, and lesion length. With these measurements, the analyst can calculate the percent diameter stenosis, lumen loss, and other parameters. The analyst is able to make qualitative observations too, such as the presence or absence of a filling defect, aneurysm, vessel perforation and dissection, and thrombus. TIMI (Thrombolysis in Myocardial Infarction trial) flow scores and frame counts are also frequently assessed by the angiographic core laboratory. The core lab analyst will report the findings. With this information, the investigator can gain insight into the safety and performance of an experimental drug or device. In addition to angiograms, angiographic core labs can utilize other programs to evaluate images obtained by other modalities, such as Intravascular Ultrasound (IVUS), and computed tomography (CT) scans.

It takes a very patient and detail-oriented individual to perform QCA. A good core lab analyst must have extensive knowledge of the anatomy and physiology of the system they are evaluating, as well as proficiency in a variety of sophisticated computer software programs. These specialized skills are learned and polished over time, and require a strong educational background and years of on-the-job experience and physician oversight. (Not to mention the ability to spend a lot of time intently concentrating on a computer screen in a dark room)! Additionally, the good core lab analyst must know when an angiogram has too poor an image quality to evaluate, for example, if the vessel contours are too blurred for accurate tracing. It is paramount that the angiographic core laboratory, investigator, and fluoroscope operator are on the same page to insure the angiograms to be analyzed are of sufficient quality for evaluation.

Hopefully, this brief summary has helped to scratch the surface of the mystery of QCA. An angiographic core laboratory can provide valuable information for the critical evaluation of potentially life-saving devices and therapies. Core lab analysts have meaningful roles in the assurance of quality and integrity of drug and device research at the preclinical and clinical levels.

At the Borgess Research Institute's Medical Device Research Laboratory, QCA can be completed as part of an in-house study or contracted separately.

References

Kern, M.J. (2003). *The Cardiac Catheterization Handbook* (4th edition). Philadelphia: Mosby, Inc. "Angiography". <http://medical-dictionary.thefreedictionary.com/p/Angiography>



A Report from Memphis- "Stick to the Script"

Margaret Coyle-Rees, Ph.D., RQAP GLP
Leifheit & Company, Inc.

I had the privilege of attending the 24th Annual Society of Quality Assurance Meeting in Memphis this past April as a scholarship recipient of the Mid-West Society of Quality Assurance Regional Chapter of the SQA. This scholarship greatly facilitated my attendance of the pre-conference training and Society meetings; I am very grateful to the Board of Directors and my fellow MWSQA members for providing me with this opportunity.

While fresh in my mind, I wanted to take this occasion to share with fellow MWSQA members my impression of the meeting. I am certain the warmer weather had something to do with my fondness of Memphis, but I found this year's conference to be very interesting. This was due largely to the lively discussions that ensued in the Advanced GLP Pre-Conference Training I attended and at the FDA and EPA regulatory update sessions. For a relative newcomer like me to QA (<10 years), these are valuable exchanges containing much useful professional information.

As noted in my scholarship letter, a big challenge for our firm has been to assist clients through the planning, execution, and completion of GLP work in OECD member countries, and states having provisional membership, all bound by different sets of regulatory requirements, for

global regulatory submissions. This is a test for any QAU professional - providing clear, concise GLP-compliance guidance in an environment of changing regulatory requirements.

While QAU is responsible for monitoring each study to assure management that supporting systems and procedures are in conformance with the GLP regulations- reviewed and discussed extensively in the training- there was an emerging theme at the meeting that resonated strongly with me. Drawing from the trainers and speakers who touched on this topic throughout the conference, there are some key challenges for QA moving forward in the global arena. Notably, QA must ensure that study plans, study conduct and reporting guidelines are carefully adhered to in light of the global regulatory climate. Regulators may have study requirements that they prescribe which diverge somewhat from GLP compliance requirements. The challenge for QA, then, is to ensure we ***stick to the script***- consistently cite the required regulations and work closely with our teams to assure compliance on every study.

I gained tremendously from speaking personally with some of the presenters after their talks. It was satisfying being able to share some of the issues I have experienced in these smaller groups, and to hear how other QA professionals have handled similar obstacles. This is one of the ***major*** benefits of attending a national SQA meeting- networking with international QA professionals, face to face, to discuss ***timely*** QAU issues relating to GLP scientific work.

Our profession benefits greatly by the continuing support of organizations like the MWSQA. I again thank the Board and MWSQA's membership, for this rewarding opportunity.

Note from your Editor

Dear Friends and Colleagues,

I am delighted to present a newsletter so full of interesting and useful articles. Think how good your name would look in the next issue of *News from the Heartland*. I hope to see your article in my mailbox soon!

Respectfully,
Paula

Paula N. Wehmeyer, Bioanalytical Systems, Inc. (BASi)
Editor, *News from the Heartland*, MWSQA newsletter

Thank You to All Who Contribute to Our Newsletter!!!

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