



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



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Please submit articles for the next newsletter by **November 26, 2008** to [editor@mwsqa.org](mailto:editor@mwsqa.org)



## ***Presidential Ponderings***

Barbara Stephenson, Pfizer, Inc.  
President, MWSQA

WOW!

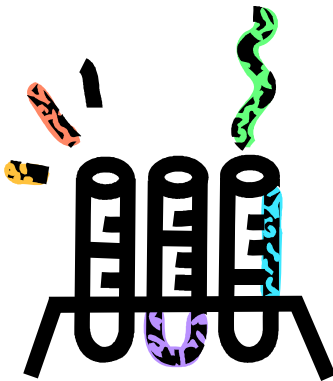
If you attended the MWSQA summer meeting in Madison at the end of July, you know what I am talking about. It was a “fabulous” meeting! The Fluno Center is a very special place. The food was good enough to add poundage. It’s a good thing the meeting was only two days long or I could have been regretting my choices. Not only was the food good, the Prairie style décor at the Fluno Center made the atmosphere comfortable and intimate. And let’s not forget the most important part, the workshops and presentations were top quality. A big “thanks” to the Planning Committee and our Planning Chair, Tim Valley (Covance Inc.), for preparing another successful meeting. We also need to thank our host Covance Inc. and each of our brilliant speakers. At last we owe thanks to our corporate sponsors Eli Lilly & Company, Pfizer, Inc. Ricerca Biosciences, LLC, WIL Laboratories, LLC, Bristol-Myers Squibb Company and MPI Research. Our host and sponsors assure we are able to have quality meetings at affordable prices. Thanks to each of you.

If you missed out on this summer’s meeting, you are in luck because we will be having another meeting in the greater Cleveland area next summer. Ricerca Biosciences, LLC will be our host for the 2009 meeting. The Planning Committee will begin planning the 2009 meeting this September. Each MWSQA member is invited to participate on the Planning Committee. Contact us to find out how. Keep an eye on the website for meeting dates so you can mark your calendar.

More good news! Now is your opportunity to run for a MWSQA office. The 2009 elections will be held this fall. Newly elected officers will begin their new term of office January 2009. We will need two new directors, a secretary and vice president. The director and secretary positions are two year terms and the vice president position is a three year obligation, first year VP, second year president and third year past president. If you would like to nominate someone or volunteer to run, please contact any member of the MWSQA Board of Directors (BoD) or our Nominations Director, Andrea Steed (Eli Lilly). E-mail addresses for all BoD members including Andrea can be found at our website, [www.MWSQA.org](http://www.MWSQA.org). Hurry and get your name on the ballot!

Remember!

Our chapter is only as good as those who volunteer to support it. Therefore, it is no surprise to me that 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.



## ***GLP Hot Topic-Test Article Presence in Bioanalytical Control Samples***

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Evaluation of systematic exposure to test articles and metabolites are typically performed as part of a toxicity assessment of new chemical entities. These evaluations are performed to demonstrate the TK/PK profile of the molecule and to serve as a verification of test system exposure. Samples of blood are collected at various intervals post-dose and the plasma is analyzed. But what about a case where test article is found in samples collected from control animals? This is a problem that is not new, but has come under increased scrutiny by the FDA and European regulators.

One method some scientists had proposed to avoid any problems was to stop collecting and/or analyzing samples from control animals altogether. Samples would either not be collected or would be discarded, without analysis. However, this approach is simply sweeping the issue “under the rug,” so to speak. One reason to collect the samples from control animals is to demonstrate that control test systems were not exposed to the test article, and were therefore appropriately dosed. Toxicity comparisons of test article-treated groups to controls may be called into question, if it is seen that the control group was exposed to the drug. TK/PK samples are frequently collected as one part of an overall toxicity study. By failing to analyze control samples, there was no independent assurance that dosing was performed according to protocol.

If control samples should be collected, how many samples are needed? Do we need to collect control samples from all study types? And if drug is found in the control sample(s), what incidence and levels are considered significant? These questions were addressed in a European Medicines Agency (EMA) Guidance entitled “Guideline on the Evaluation of Control Samples in Nonclinical Safety Studies: Checking for Contamination with the Test Substance,” effective September of 2005.

The Guidance recommends control samples be collected from all pivotal studies with a toxicokinetic evaluation. For non-rodent studies, control samples should be collected and analyzed in the same way as treated samples. For rodent studies, control samples should be collected and analyzed at least in the vicinity of T<sub>max</sub> of the test substance.

The Guidance also states “Trace levels of contamination that are below the lower limit of quantification may in principle be considered as nonrelevant.” Additionally, the data from controls should be reported as a part of the toxicokinetic report.

In instances where test article concentrations are found in control samples, it is important to conduct an investigation. The study director must be notified of the investigation and any results. An evaluation of the impact on overall study results must be documented in the data

and final report. The investigation should focus on determining if the contamination is *in vivo* or *ex-vivo*. *In Vivo* contamination may call the validity of the entire study into question. *Ex-vivo* contamination may compromise the TK/PK results.

It is a good policy to have a standard operating procedure in place to describe the typical methodology taken to determine the cause of any contamination. The SOP should describe the methods of determining *in-vivo* contamination (i.e. presence of plasma metabolites, antibodies, or frequency/distribution of concentrations). Additionally, a description of methods of examining the Bioanalytical method and analytical techniques for *ex-vivo* contamination (i.e. sample handling, carryover effects, frequency/incidence of contamination, etc.) should be defined. Any requirement for sample re-analysis should be pre-defined in the SOP and the method of reporting described.

SOPs for animal handling, sample collection and processing should be reviewed to ensure that appropriate precautions are taken to prevent cross-contamination. Certain test articles/routes of administration (i.e. dermal studies) are more prone to contamination. Changing gloves, using separate centrifuges, etc. may be needed to minimize the possibility of cross-contamination. Collection of samples from control animals before treated animals should also be considered. Physical separation of animal caging should be appropriate to preclude material being transferred from drug-treated animals to control animals. With certain test articles and study types (i.e. dermal) it may be necessary to have control groups placed in a separate area or room.

The use of modern Bioanalytical equipment, such as Mass Spectrometry allows for increased detection of molecules at ever lower concentrations. As a result, it is now more important than ever to make sure proper procedures are in place to preclude contamination. If test article is nevertheless detected in control samples, a procedure for conducting an investigation and the appropriate documentation in the data and report will help to provide assurance to the regulatory agency reviewers of study integrity.



## **Summer Memories**

Timothy Valley, Covance Laboratories, Inc.  
MWSQA Vice President and Planning Chair

The Summer MWSQA meeting has come and gone, much like summer itself. Those that attended the meeting recall fond memories with friends and colleagues, informative sessions, excellent training workshops, and delicious food. The planning committee would like to thank all the individuals that contributed to the workshops or presented during the meetings. Without their dedication and support the conference would not be possible. A special thanks to Michael Keherly and Stephen Rogenthien for pulling together the most attended workshop with very little advance notice.

The planning committee would also like to thank all those that attended the meeting as well as our sponsors. Without your attendance or financial support such meetings would not be

possible. Our sponsors include Covance Laboratories Inc, Eli Lilly and Company, Pfizer, Inc, Ricerca Biosciences, LLC, WIL Research Laboratories, LLC, Bristol-Meyer Squibb Company, and MPI Research.

The meeting began bright and early Tuesday with registration and three workshops. Topics included the role of the study director, computer system validations, and problem-based GLP learning. Preliminary survey results have been positive for each one. Late in the afternoon we heard from Barb Stephenson, President of MWSQA. Barb's welcome address included little known facts about the state of Wisconsin, and set the stage for the rest of the meeting. John Yergler provided an SQA update. Matt Foster provided an update from the task force on modernization of GLPs.

Soon after completion of the meetings opening presentations Tuesday evening the buses left for the Madison Mallards baseball game. The MWSQA attendees found a lively crowd in the Duck Blind with pre-game festivities in full swing. As the game got underway, the skies darkened and eventually rain set in. Not to be deterred, many stayed until after nine o'clock taking advantage of all the food and refreshments that were available.

Wednesday morning kicked off with Kim Colangelo (Associate Director for Regulatory Affairs, Office of New Drugs, CDER, FDA) providing an update on CDER and in particular the recently implemented FDAAA (Food and Drug Administration Amendments Act of 2007). The presentation was informative and very well received. All questions were welcomed and answered by Kim.

The remainder of Wednesday included 12 very relevant speaking sessions. Topics ranged from test article characterization, incurred sample reproducibility, GCP documentation practices, to computer validation practices.

As I look back on the meeting I'm pleased with the outcome. With the exception of the rain during the Mallards game, everything went as planned. The Fluno Center and its staff provided an excellent venue and all the support needed for the meeting. I could not have asked for more. I would also like to thank the entire planning committee for their dedication and hard work.

### ***Note from your Editor***

Dear Friends and Colleagues,

It's hard to believe that summer is nearly over. Now that the weather keeps us indoors more, maybe it will be easier to settle down at your desk and write an article for this, *your* news letter. There are so many critical aspects to the work we do and so many excellent minds out there, surely you are one of the people who have some good ideas or useful insights to share. Please help keep this newsletter a useful resource to help us in our quest for quality.

In Service,  
Paula

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Editor, *News from the Heartland*, MWSQA newsletter

**Thank You to All Who Contribute to Your Newsletter**

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