



# erings

Volume 9 Issue 1

March 2003

## ***From the Editor's Desk***

Greetings MATT Members;

The format for the Newsletter has been altered for this edition to accommodate some business that we have to deal with. Chris Goodall has been working with the Executive Committee to overhaul the By-Laws and space has been provided so that the membership can review the prospective changes prior to the Spring Meeting.

Speaking of Chris, she will soon be an Ex-President and she deserves a great deal of credit for her commitment to keeping this Organization afloat.

**Thanks Chris!!**

See you all in East Lansing!

There when it sMATTers most!

Fred

## **President's Korner**

This is my parting message. It has been a pleasure to serve as President of MATT and though I will no longer compose this column, I plan to stay involved and support the continued growth of the organization. First, let's talk business.

The membership renewal form for 2003 is included for your convenience. If you have not submitted your renewal, please do so soon. At the time I prepared this message, renewals were less than 40%. Note that we will not be issuing membership cards with the renewals. We have kept the membership renewal at \$20 but must watch our expenses to do so. Of course, if you need a receipt, just include a note with your renewal, and the Treasurer will provide confirmation of payment.

In addition, the time has come for an update to the MATT by-laws. The Executive Board has reviewed the by-laws carefully and recommended changes that are necessary. We will vote on these changes at the members meeting in May. The Board has approved the changes published here. There is still time to suggest additions or revisions, but only if the Executive Board has time to review them before the annual meeting. We will not accept any changes at the meeting. Please forward your ideas to me by email as soon as possible.

By now, you know a bit about my background and interests. I would like to use this opportunity to recognize and thank the members of the Executive Board who have been active in continuing and promoting the goals of our organization.

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*MATT is an association focused on advancing the scientific, clinical, professional, and educational aspects of Toxicology and TDM. MATT provides a network for interested individuals in the Midwest.*

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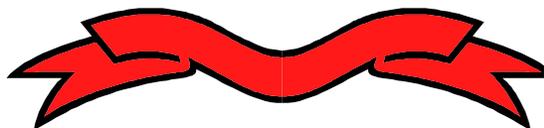
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## **EXECUTIVE COMMITTEES**

### 2001-02 Executive Committee

Christine Goodall, B.S.C., President (WI)  
Adam Negrusz, Ph.D., Vice President (IL)  
Dan Isenschmid, Ph.D., Advisory Board Chairman (MI)  
Laureen Marinetti, M.S., Secretary (MI)  
Tim Caragher, Ph.D., Treasurer (IL)  
Fred C. House, sMATTERings Editor (MI)



## Lifetime Members

*John C. Baenziger, M.D.,*  
Indiana University School of Medicine  
*Larry D. Bowers, Ph.D.*

*Michael E. Caplis, Ph.D.*  
Great Lakes Laboratories  
*Larry B. Plutchak*  
Utak Laboratories  
*John M. Wilson, Ph.D.*  
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Great Lakes Laboratories  
*Larry B. Plutchak*  
Utak Laboratories  
*John M. Wilson, Ph.D.*  
William Beaumont Hospital  
*Steven H. Wong, Ph.D.*

**Adam Negrusz**, Vice President, was awarded tenure at the University of Illinois at Chicago in 2002. Congratulations! Adam continues to advance the field of Toxicology as a professor and researcher. His focus is in the area of drug-facilitated sexual assault and the development of state-of-the-art chromatographic methods for analysis of varied types of biological samples. Adam is active professionally and has numerous publications to his credit. Adam has a fondness for good cigars.

**Laureen Marinetti** is currently a PhD candidate, having recently completed a course of research and study at Wayne State University. Laureen focused her research in the area of drug pharmacology. (She's all the rave!) She recently moved into the position of Chief Toxicologist at the Montgomery County Coroner's Office in Dayton, Ohio. Laureen is promoting our profession by co-hosting the annual MATT meeting in East Lansing in May 2003. Don't miss it!

**Tim Caragher**, Treasurer and practicing Clinical Chemist, provides clinical focus and expertise to our organization. He continues to enhance our profession through training Medical Technology students. He has worked with numerous manufacturers in the development of the laboratory assays that we use. He has numerous publications to his credit and continues to look to the future of the laboratory pursuing interests in Point-of-Care testing and Molecular Diagnostics. We call Tim moneybags, as he serves as Treasurer in multiple professional organizations.

**Fred House** frequently refers to himself as a lab rat. Nothing could be further from the truth. As an employee of the Lansing Forensic Laboratory, Fred is always at the forefront in our continuing efforts to keep our highways safe. Twice a year he organizes and publishes sMATTERings, the newsletter of MATT. In addition, he has been active in maintaining our membership database. Fred is responsible for organizing our annual outing to a pool hall when the business day is done.

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**CANDIDATES FOR 2003 ELECTION**

**President:**

Laureen Marinetti (1 year term)

**Vice-President:**

Barbara Rowland (1 year term)

**Secretary:**

Don Frederick ( 2 year term)

**Treasurer:**

Tim Caragher (this is a 2 year term, but Tim has been Treasurer for a year already).



The concept is that in order to provide continuity, the Treasurer will become VP in 2004, then Secretary in 2005, the Treasurer etc. so the 2 year terms will stagger to the VP position. Both President and VP will be one year terms.

**NOTICE! NOTICE! NOTICE!**

Information updates with regard to the upcoming MATT meeting in East Lansing can be obtained by visiting the MATT Website @ [www-midwesttox.org](http://www-midwesttox.org)

*Dan Isenschmid*, Advisory Board Chair, has been active in MATT for many years. Dan is an expert in many areas, as he serves on the Editorial Advisory Board for the Journal of Analytical Toxicology. In addition, he deserves accolades for co-hosting SOFT 2002 in Detroit. The meeting was excellent! In addition to excellent scientific knowledge, Dan is our food and wine connoisseur.

*Christine Moore*, Past-President, actively contributes in the field of neonatal testing and methods involving alternate sample types. Her most recent work in the area of fetal alcohol syndrome can be seen in Volume 49 of Clinical Chemistry. She has numerous publications to her credit. She is one of my favorite workshop presenters. If you have a chance to see her speak, don't miss it. Being English, she also knows how to find really good beer.

And also, a special thanks to Kristen Akey, the lovely lady who set up and maintains our Web site ([www.midwesttox.org](http://www.midwesttox.org)).

There you have it, just a sample of the talent and expertise that our group brings to the profession. The lifetime members, former officers and membership as a whole, offer unlimited resource to the toxicologist, whether clinical or forensic. As I move on, I hope I have encouraged your interest in continued involvement with MATT.

*Come join us in East Lansing, May 8-9, 2003.*



## Bylaws Of The Midwest Association For Toxicology and Therapeutic Drug Monitoring (MATT)

### Article I: Name and Objectives

#### Section 1: Name

The Name of this organization is The Midwest Association for Toxicology and Therapeutic Drug Monitoring, and may herein be referred to as the Association or MATT. **The Association shall be incorporated as a non-profit scientific and educational association in the State of Ohio. (Delete the underlined phrase).**

#### Section 2: Goals and Objectives

The Goals of the organization are: to advance the scientific, research, clinical services, and education in Toxicology - Clinical, Forensic, environmental and others, and Therapeutic Drug Monitoring; and to develop a membership from interest **of (add)** fellow scientists, physicians, health professional, administrators and industrial colleagues. The Objectives are: to promote the professional, scientific and educational activities through planned meetings and symposia; to develop and distribute newsletters for the membership; to form specific interest-focused groups for enhancing their professional and scientific activities; to interact/collaborate/enhance professional, research and educational activities with other professional organizations.

### Article II: Region and Headquarters

#### Section 1: Region

The Region of the Association will consist of the states of Wisconsin, Illinois, Indiana, Ohio, Michigan and Minnesota. **(Expand the region to include Iowa, Kansas, and Missouri).**

#### Section 2: Headquarters

The Headquarters of the Association will be at the business address of the President.

### Article III: Members, Privileges, Rights, Responsibilities, and Applications

#### Section 1: Members

Members shall be persons who work or have interest in the fields of Toxicology or Therapeutic Drug Monitoring **or Pharmacogenomics. (add)**

#### Section 2: Student Members

Student Members shall be persons who are actively involved in formal education or training programs in the fields of Toxicology or Therapeutic Drug Monitoring and are not considered employees in these programs. Student Members may not vote, hold office or participate in the business meetings of the Association. They shall pay dues as designated by the Association. Student Members will receive official communications (newsletters, meeting notices, etc.) similar to those received by Members.

#### Section 3: Honorary Members

Honorary Members may be designated from time to time by the Executive Board. These persons shall have served the Association through either direct contribution of service or through contributions to the advancement

of the fields of Toxicology or Therapeutic Drug Monitoring. Honorary Members shall not pay dues, vote, hold office or participate in the business meetings of the Association. Honorary Members will receive Association services as defined by the Executive Board.

#### **Section 4: Advisory Board Members**

Advisory Board Members shall be appointed by the Executive Board and shall be persons with specific expertise or experience in the fields of Toxicology and Therapeutic Drug Monitoring, who shall act as an advisory group to the Executive Board and the Association. Advisory Board Members are not required to be members of the Association or live in the region. Advisory Board Members who are not members of the Association shall not pay dues, vote, hold office or participate in the business meetings of the Association. *(delete this Section).*

#### **Section 5: Privileges and Responsibilities of Members *(becomes Section 4)***

Membership in the Association is considered a privilege and is dependent on persons complying with the Bylaws and following high standards of professional ethics and practice. Members are expected to contribute to the objectives of the Association. Members will receive services or benefits such as newsletters, meeting notifications, meeting discounted registration fees, etc., as are defined by the Executive Board.

### **Article IV: Dues and Delinquency**

#### **Section 1: Dues**

The Dues for membership in the Association will be determined annually by the Executive Board. These Dues will be payable on or before December 1 for the current year. Payment of dues will be considered delinquent after December 31 of the current year.

#### **Section 2: Delinquency**

Failure to pay membership dues may result in loss of membership services provided by the Association. The person's name will be removed from the official membership list. Delinquency of payment of dues will eliminate the member from his/her ability to serve as an officer or as a candidate for office or member of the Executive Board. *(delete)* Delinquency of dues payment is considered grounds for removal of an officer or member of the Executive Board. Re-instatement after removal of a member's name from the official membership list requires reapplication for membership to the Association.

### **Article V: Officers, Executive Board: Qualifications, Duties, Term of Office**

#### **Section 1: Officers and Executive Board**

Officers of the Association shall be elected by the members and members-at-large and shall consist of a President, Vice President, Secretary-Treasurer and Chairman of the Advisory Board. The Executive Board shall consist of all elected Officers, the Chairman, the Advisory Board, and the immediate Past President.

*(Replace with:)*

*Officers of the Association shall be elected by the members and members-at-large and shall consist of a President, Vice President, Secretary, and Treasurer. A Newsletter Editor and Web Page/Membership Chair shall be appointed by the President. The Executive Board shall consist of all elected Officers, the Newsletter Editor, the Web Page/Membership chair and the immediate Past President. Only the elected Officers and the immediate Past President will have voting rights in regard to Executive Committee decisions. The Newsletter Editor and Web Page/Membership chair may be present at all meetings in an advisory manner but will not be included in determining a quorum of the Executive Board.*

## Section 2: Qualifications

The Officers and Executive Board shall be members of the Association.

## Section 3: Duties of the Executive Board

The Executive Board shall be the legal governing body of the Association.

The Executive Board shall have complete control and management of the affairs of the Association as is defined by law and by these Bylaws. The Executive Board shall approve the appointment of Chairs of Standing Committees, (delete) Ad-hoc Committees, Members of the Advisory Board, (delete) or any other group that is required to conduct the business or accomplish the objectives of the Association.

## Section 4: Duties of the Officers

**President:** Shall be the President of the Association and the Chairman of the Executive Board. Shall preside at all meetings of the members as well as the Executive Board. Shall be an ex-officio member of all committees, except the Nominating committee. Shall appoint Chairpersons and Members of Standing Committees with approval of the Executive Board and except where otherwise designated by these Bylaws (delete). ***Shall appoint a Newsletter Editor or Web Page/Membership Chair should the positions be vacated or the officers removed from their position. (Add)*** Shall appoint Ad-Hoc Committees when necessary with approval of the Executive Board. Shall perform all other duties assigned to him/her by the Executive Board. Shall become the immediate Past-President upon completion of the term of office.

***Past-President: The immediate Past-President will remain as a voting member of the executive board for one year after completion of term of office as President. The Past-President is responsible for the Nominations committee and the proper presentation of candidates prior to the annual meeting. (ADD)***

**Vice-President:** Shall perform the duties of President when the President is unable to perform his/her duties. Shall perform all other duties assigned to him/her by the Executive Board.

**Secretary:** Shall keep accurate and permanent records of all Executive Board meetings and Association meetings. Shall maintain an accurate membership list, (delete) Shall answer Association correspondence promptly and keep files of the same.

**Treasurer:** Shall keep accurate and timely financial records including all receipts of monies, expenditures, disbursements and accounts receivable of the Association. Shall maintain the bank account for the Association's funds and provide monthly statements of accounts to the Executive Board. Shall deposit all monies received by the Association. Shall make all payments as directed by the President or the Executive Board. Shall provide a yearly financial statement to the Association members at the annual meeting, and provide financial statements required by federal and state agencies.

***Newsletter Editor: The President will appoint The Newsletter Editor. A term of office is not defined. The Editor can be removed by vote of the Executive Board. The Newsletter Editor serves in an advisory capacity on the Executive Board but does not have voting rights in Board decisions. The Editor is responsible for the publication of two newsletters per year on the schedule affirmed each year by the Executive Board. (ADD)***

***Web Page/Membership Chair: The President appoints the person in this position. A term of office is not defined. The Chair can be removed by vote of the Executive Board. The Web Page/Membership Chair serves in an advisory capacity on the Executive Board but does not have voting rights in Board decisions. The person in the position is responsible for collecting membership renewals and maintaining a current list of the membership, including an email directory. The person is responsible for notification of dues past due. The Web Page must be managed and kept current, properly reflecting the annual meeting information and other activities of the organization as directed by the Executive Board. (ADD)***

Section 5: Term of Office

Each Officer or Member of the Executive Board shall be elected on a bi-annual basis by a majority vote of the membership. Each Officer or Member of the Executive Board will serve a two-year term. Each Officer or Member of the Executive Board will take office effective as of December 1 or serve until their respective successors have been elected.

*(Replace with:)*

***Each Officer of the Executive Board shall be elected by a majority vote of the membership. Starting in 2003, the President and Vice-President serve a one-year term. The Secretary and Treasurer will serve a two-year term, and be elected in alternate years. The Treasurer elected in 2003 will serve a one-year term. Each Officer or Member of the Executive Board will take office immediately following the Annual Meeting.***

**Article VI: Removal From Office, Removal of Membership, Appeal**

Section 1: Removal from Office

Any Officer or Member of the Executive Board can be removed by a vote of the Executive Board at a regular or special meeting (three out of four votes for the first two years, and three out of five votes thereafter ***are required for removal.*** ***(remove and add)*** The reasons for the proposed removal must be sent to all Members of the Executive Board at least thirty days prior to any meeting that will vote on removal of any Officer or Executive Board Member. The termination of an Officer or Members position will be effective immediately after the vote.

Section 2: Right of Appeal

Any person removed from the Executive Board may appeal this removal by submitting within thirty days, a written request of an appeal to the Executive Board. This appeal will be reviewed as a specific agenda item during the next scheduled meeting of the Membership. The appeal will be formally presented and a secret ballot of Members present (a quorum must be present) will be taken. A two-thirds (2/3) vote will be required to re-instate the Officer or Member of the Executive Board.

**Article VII: Meetings: Regular/Special of the Executive Board and Membership  
Quorum and Parliamentary Rules**

Section 1: Regular Meetings of the Executive Board

The Executive Board must meet at lease quarterly either in person or through conference calls. A quorum shall consist of at least three of the four Board Members during the first two years of the Association's existence, or three of the five Board Members thereafter.

***Replace With:***

***The Executive Board must meet at least annually either in person or through conference calls. A quorum shall consist of three voting Board Members.***

Section 2: Special Meetings of the Executive Board

Special meetings of the Executive Board may be called by any Member of the Executive Board with a thirty-day advanced notice being given to all members of the Board.

Section 3: Regular and Special Meetings of the Membership

The Association shall hold at least one annual meeting of the Membership. Special Meetings of the Membership may be called by the President with approval of the Executive Board or by the Membership with the submission of a petition from at least 10% of the membership requesting a special meeting. Thirty-day advanced notice must be given to all members of the Association of the Special Meeting, including the purpose and agenda for the meeting. A quorum of a meeting of Membership shall consist of at least 20 members of the Association. ***the number of members present at the Annual Meeting.*** ***(remove and replace)***

Section 4: Parliamentary Rules and Rules on Quorums

All meetings of the Executive Board and Membership shall follow the Parliamentary Rules as detailed by the most recent edition of Robert's Rules of Order. A three-quarters (3/4) vote of the members present is required to suspend the Parliamentary Rules. If Quorums are not present at the meetings of the Executive Board or meetings of the Membership, only discussions and recommendations concerning a meeting's agenda may occur and no official action can take place.

**Article VIII: Nominations, Elections, Voting and Vacancies**

Section 1. Nominations

The Nomination Committee shall submit a proposed slate of Officers and Elected Members of the Executive Board each year. In addition, Nominations must be solicited from the Membership of the Association at least 30 days prior to the closing of nominations for annual elections of the Association.

Section 2. Elections

Elections of Elected Officers and Members of the Executive Board shall occur each year **at the annual meeting.** **(Add)** Election of Executive Board Members or Officers will consist of a majority vote by the Membership **present at the meeting. (Add)**

Section 3: Voting

Voting shall occur by secret ballot, performed during either at an annual meeting of the Membership or through mailed ballots. Elections that occur at meetings of the Membership must be preceded by at least a thirty-day advanced notice to the Membership that elections will occur at the Membership meeting. Voting occurring by mailed ballots shall be done at least thirty days before the next meeting of the Membership. Sealed ballots shall be returned to the Secretary-Treasurer and be opened and counted at the next meeting of the Membership by a Ballot Committee which will consist of at least three members appointed by the President. Ballots must be maintained for at least one year after the election. Tie votes will be decided by a majority vote of the Executive Board. All elected officers will take office immediately after the annual membership meeting.

**Replace with:**

**Voting shall occur by secret ballot or by acclamation, at the annual meeting of the Membership. Elections must be preceded by at least a thirty-day advanced notice to the Membership that elections will occur at the Membership meeting. Tied votes will be decided by a majority vote of the Executive Board. All elected officers will take office immediately after the annual membership meeting.**

Section 4: Vacancies

The Executive Board by majority vote shall fill any vacancy of the Executive Board that occurs before expiration of the term of the Executive Board Member.

**Article IX: Committee Appointments, Standing, Ad Hoc, Duties**

Section 1: Appointment of Committee Chairpersons and Members

The newly elected President shall within thirty days of taking office submit to the Executive Board for its approval, his/her recommendations for **the Chairperson and Members of all Standing (delete)** Committees, except the Nomination Committee. It is understood that the submitted list of persons are Members of the Association and that they have agreed to serve on the committees. The Chairperson and Members of each **Standing (delete)** Committee shall serve for one year or at least until their successors are approved by the Executive Board.

Section 2: Standing Committees

Standing Committee(s) of the Association shall consist of the Nomination Committee, the Bylaws Committee, the Advisory Board, the Membership Committee, the Newsletter or Publication Committee, and the Education Committee (*delete*). The Nomination Committee will be chaired by the immediate Past President (or until there is a Past President by a Member of the Association appointed by the Executive Board to serve in this office) (*delete*) and will consist of at least two other Members of the Association, which are appointed and (*delete*) approved by the Executive Board.

The Advisory Board will be chaired by the elected Chairman of the Advisory Board and the Members of the Advisory Board shall be approved by the Executive Board. The Chairperson of the Newsletter or Publication Committee will be the Editor of the Newsletter unless, another person is appointed by the Executive Board. (*delete*)

### Section 3: Ad Hoc Committees

The President may appoint Ad Hoc Committees to work on specific tasks as necessary. The Ad Hoc Committee will be dissolved with the end of the President's term of office.

### Section 4: Duties of Committees

The Executive Board shall define the duties and responsibilities of each Committee, unless specifically defined by these Bylaws.

## **Article X: Amendments of Bylaws**

Any Member of the Association may submit amendments to these Bylaws. The proposed amendments will be submitted to the Bylaws Committee for discussion and recommendation to the Executive Board. The Executive Board will approve or disapprove the proposed amendment for Bylaws. If approved, the Executive Board will submit the proposed amendment to the Association's membership for approval. Membership voting on Bylaws amendments shall follow the same processes as used for election of officers. If the Executive Board disapproves the amendment, the amendment may be brought to a vote of the Membership by the submission of a petition of at least 10% of the Membership. Such a petition must be considered at the next scheduled meeting of the Membership.

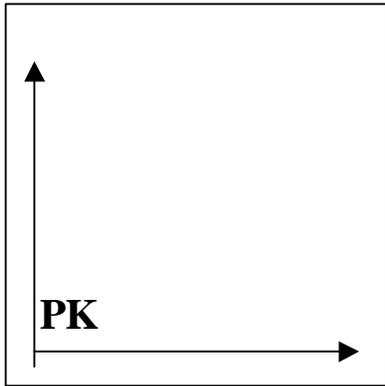
## **Article XI: Termination of Association, Disposition of Records, Resources and Monies**

### Section 1: Disposition of Records

If the Association is formally dissolved as a non-profit scientific corporation, then all minutes, books, documents, materials, and records will be donated to the Society of Forensic Toxicology, unless their disposition is directed otherwise by the Executive Board.

### Section 2: Disposition of Monies

If the Association is formally dissolved as a non-profit scientific corporation, then all monies and resources will be donated to the Society of Forensic Toxicology, unless their disposition is directed otherwise by the Executive Board.



# Pharmacokinetics Korner

By John M. Wilson

## Limited Sampling Strategies – What Does it Mean?

In the last several years there has been increased interest in LSS or Limited Sampling Strategies for a number of important, routinely monitored drugs, such as Cyclosporine<sup>1,3</sup> and Tacrolimus, and some not so commonly monitored drugs, such as Mycophenolic Acid and Busulfan.<sup>2</sup> The interest in LSS provides some important insights into the application of pharmacokinetics to therapeutics so I thought it might be worth a little summary.

It was a long held view that pharmacokinetics and clinical therapeutics were not that compatible, at least as it applied to the use of analytical drug measurements and the determination of individual pharmacokinetic parameters that could be used to establish the appropriate dosing regimen for a patient. The argument was made that in order to define the pharmacokinetics for a drug in an individual it was necessary to select a pharmacokinetic model, give a known dose, intensively sample biological concentrations over the post-dose period, and then mathematically fit the data to the model to determine values for the pharmacokinetic variables. **The practice of therapeutics settled on determination of a single concentration that correlated to the therapeutic or toxic effect. For most analytes this was defined as a trough concentration at steady-state.** It's fair to say that TDM as it is commonly practiced exemplifies LSS.

The value of the trough concentration was that it minimized pre-analytical variability. Collecting a sample just before the next dose administration was an intuitive idea and easy to put into practice. Of equal importance is that the trough value shows less biological variability in that, once steady-state is achieved, trough values should remain constant from dose to dose as long as the dose and the dosing interval remain unchanged. It is valuable that the pharmacokinetic model for a drug given orally and exhibiting one-compartment characteristics can be used to predict the concentration of drug in the serum at any time after a single dose. The dose and bioavailability of a drug, the volume of distribution, and both the absorption and elimination of a drug will influence the concentration. This relationship is described by<sup>4</sup>

$$C = \frac{k_a FX}{V(k_a - K)} (e^{-Kt} - e^{-k_a t}) \quad 1)$$

where C is the concentration at time t, V is the volume of distribution, F is the bioavailability, X is the dose, and  $k_a$  and K are the absorption and elimination rate constants, respectively. It is generally true that  $k_a$  takes a larger value than K, so that, in the post-absorptive state, the exponential term containing  $k_a$  will become zero and the equation simplifies to

$$C = \frac{k_a FX}{V(k_a - K)} e^{-Kt} \quad 2)$$

While  $C_t$  or the trough concentration still depends on bioavailability and  $k_a$  in most situations, when  $k_a$  is very much larger than K, the equation further simplifies to

$$C_t = \frac{FX}{V} e^{-Kt} \quad 3)$$

leading to the conclusion that **trough concentrations vary less because they are dependent on fewer variables**. There are relatively few instances when peak concentrations are preferred over troughs. The only one that I am aware of is Theophylline due to its low seizure threshold and the interest in maintaining concentrations in children below the threshold. More recently there has been an increased interest in measuring peak levels when there is an interest in characterizing the area under the concentration-time curve or AUC.

Peak concentration can be calculated from equation 1 but this requires knowledge of absorption rates and bioavailability which can vary in an individual due to meals, co-administered drugs, and the pH of the gut. The time to peak for a drug given orally is described as<sup>4</sup>

$$t_{\max} = \frac{1}{k_a - K} \ln \frac{k_a}{K} \quad 4)$$

The time at which peak concentrations occur is a function of both the rate constants of elimination and of absorption. If the absorption rate constant is greater than the elimination rate constant [a reasonable assumption] then, **for a fixed elimination rate constant, decreasing the value of  $k_a$  will increase the time to peak concentration**.

The value of AUC is that it represents a measure of exposure. Trough concentrations have been useful for the purpose of monitoring, because reproducibility offers advantages when patients are compared against themselves on a daily basis and they can be used to establish a link between dose and effect. But there are areas when therapy and/or toxicity is cumulative and steady-state trough levels, by virtue of their stability, may not adequately reflect the underlying phenomena. Specific areas such as chemotherapy for cancer or infectious disease or in immunosuppression have frequently encountered difficulties in relating a given effect with a single timed concentration. This is consistent with our own experience with Cyclosporine.<sup>5</sup> We were not able to show serum relationships to toxicity or rejection until we looked at average Cyclosporine concentration for the 2 weeks before the event. In theory, the farther removed the effect is from the serum compartment and the more the drug is concentrated in tissues the less useful are trough concentrations. It is not surprising then that chemotherapy and immunosuppression have been significant for the use of LSS in the estimation of AUC.

Many of the publications have attempted to estimate AUC by measuring 2, 4 or even 6 levels.<sup>1</sup> Somewhat better luck has come from attempting to find a single level that correlates with the AUC. Most commonly, as in the case of Cyclosporine, that level is the peak level.<sup>3,6</sup> For Cyclosporine that appears to require a sample drawn at two hours, or the C2 concentration.<sup>3</sup>

The application to Cyclosporine may provide special insight into some of the issues for us. This is a drug that is very poorly absorbed. According to equation 1 peak levels are influenced to a significant degree by the rate of absorption and the relative magnitude of the absorption and elimination rate constants. Recently, a new formulation of Cyclosporine has become available that increases the rate and extent of absorption. Unfortunately, this also increases the variability. Cyclosporine appears to be a substrate for the P-glycoprotein transporter system and for CYP3A4. P-glycoprotein is a protective mechanism that prevents the transport of molecules from the intestinal tract into the systemic circulation. It effectively holds Cyclosporine in the cells of the gut wall and returns it to the gut. CYP 3A4 is an oxidative enzyme of the cytochrome P-450 family that is found both in the gut and the liver. Oxidation by CYP3A4 for an oral drug will be pre-systemic; the effect of this is that the body will see inactive metabolites rather than active parent substance. In both cases less drug will enter the body. Any variability in affinity for CYP 3A4 and for the P-glycoprotein receptor will add to the variability in the pharmacokinetics of the drug affecting both the rate and magnitude of absorption. TDM is often more important for a drug with poor bioavailability because of this lack of predictability. When a drug is 95 %, or almost completely, absorbed, a change of 5 % will have little impact on serum plasma levels. But a 5 % change for a drug with 5 % bioavailability represents a 100 % change and makes a significant clinical difference. Measuring a peak level provides more insight into this variability.<sup>3</sup>

If we are convinced that a peak level gives us a better sense of how much drug is absorbed and that AUC is a better measure of the body's exposure to the drug then the issue reverts to how to monitor in order to maximize our information. It might help to know how AUC relates to other pharmacokinetic variables. There are a variety of ways to estimate AUC. I will segregate them according to whether they are dependent on the assumption of a pharmacokinetic model or whether they are model-independent. An example of an approach that is model-independent is to draw many samples over a dosage interval and to use the trapezoidal rule to calculate the area under the curve. An example of the former approach would be to assume a one-compartment, concentration-dependent absorption model and to integrate from time 0 to time infinity,  $AUC = \int_0^{\infty} C dt$ , where C is represented by equation 1. This produces the following expression for AUC in terms of pharmacokinetic parameters:

$$AUC = \frac{FX}{VK} \quad 5)$$

and the startling conclusion that **AUC depends on extent of absorption but not rate** and that **the elimination rate constant will influence AUC but not the absorption rate constant**. This may be easier to envision if it is considered that, to influence the concentration, it is only important for a drug molecule to get into the body not how fast it gets into the body. Concentration will also be influenced by how long the drug molecule stays in the body. Absorption rate really is concerned with a concentration in a depot site that is not a part of the AUC. **The value of C2 Cyclosporine is that it is a better estimator of bioavailability, F, than the trough concentration.**

In this context it is possible to imagine that, since a trough concentration is related to elimination, as with equation 3, that there should be a correlation between trough concentrations and AUC. Though this may be the case, in practical terms, it probably will be a weak correlation due to the exponential relationship of concentration and time and the relative lack of area under the elimination portion of the AUC. This is borne out in Pedersen's analysis<sup>6</sup> that suggests that, for a single estimator, the best theoretical choice is likely to be the concentration at the peak, regardless of what time this represents. These points together suggest why many of the methods for estimating AUC from a few fixed time points will choose a peak and a trough level and, sometimes, additional levels. The difficulty is that variation in peak time and in the concentration measurements will contribute error to the relationship. C2 still seems like a pretty good approximation of the peak level for this type of approach.

A third possibility is to utilize a Cyclosporine model that weights the few available data points with data about the population as a whole. This is referred to as a Bayesian approach.<sup>7</sup> It assumes error in analytical measurement, in absorption, clearance and volume of distribution and adjusts the average relationship between dose and concentration over time to encompass the patient data. Any data that permits a helpful adjustment to the data can be added such as age, height, weight, or renal function. This is a model-based approach and will be satisfactory as long as the patient adheres reasonably to the model. As is generally the case, the more data available for the fit, the more confidence that can be placed in the result.

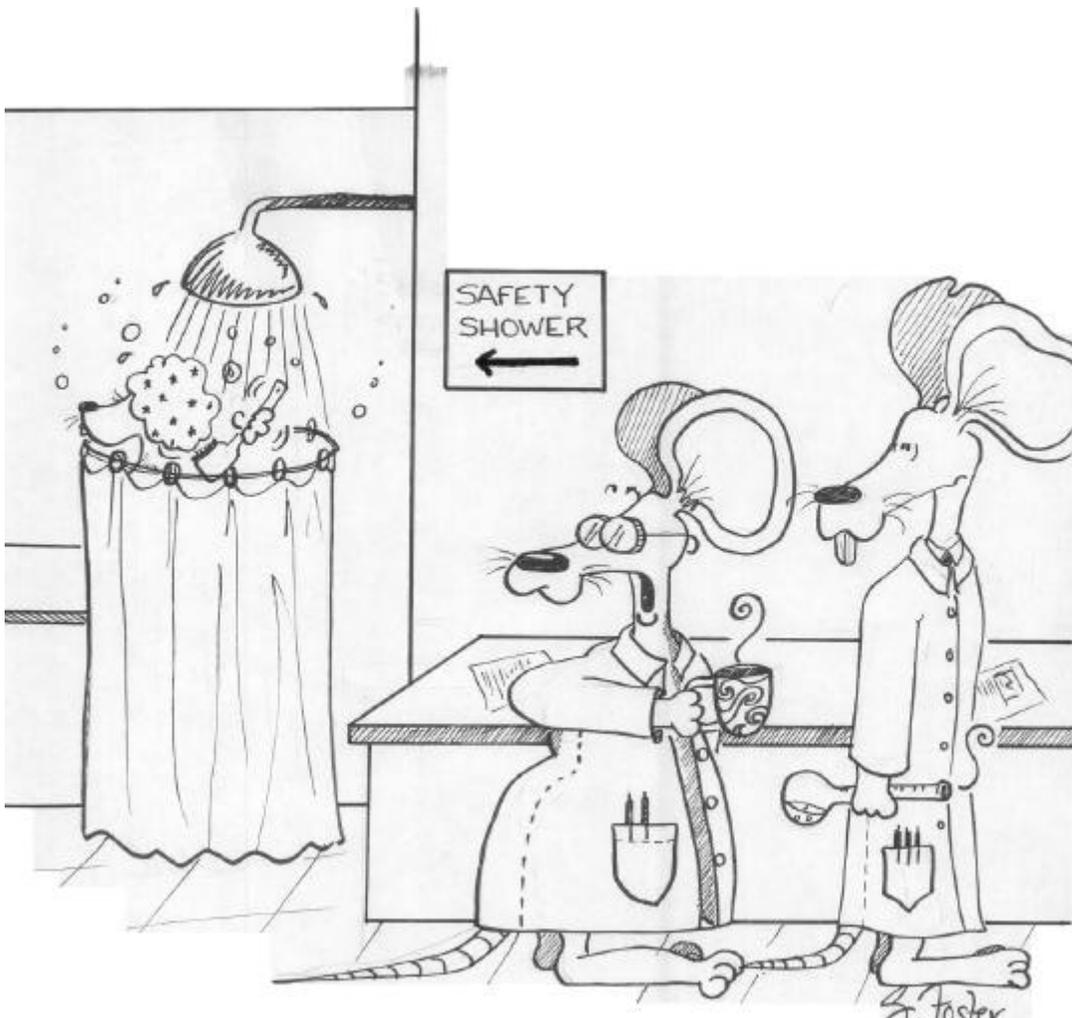
Certainly there will be advocates of continuing the use of trough measurements exclusively for monitoring Cyclosporine patients just as certainly there will be those who find added benefit to peak concentrations [for one thing the peak levels are much higher and easier to measure accurately by chromatographic means]. My opinion is that both measurements, combined with Bayesian control, will produce an outcome that is superior to the others and I look forward to papers appearing in the future that will demonstrate this.

#### References:

1. David OJ, Johnston A. Limited Sampling Strategies for Estimating Cyclosporin Area Under the Concentration-Time Curve: A Review of Current Algorithms. *Therap Drug Monitor*, 23:100-114, 2001.
2. Tabak A, Hoffer E, Rowe JM, Krivoy N. Monitoring of Busulfan Area Under the Curve: Estimation by a Single Measurement. *Therap Drug Monitor* 23:526-528, 2001.
3. Oellerich M, Armstrong VW. Two-Hour Cyclosporine Concentration Determination: An Appropriate Tool to Monitor Neoral Therapy? *Therap Drug Monitor* 24:40-46, 2002.
4. Gibaldi M, Perrier D. *Pharmacokinetics*, 2<sup>nd</sup> Ed. Revised and Expanded. Marcel Dekker, New York, 1982.
5. Khauli RB, Wilson JM, Baker SP, Valliere SA, Lovewell TD, Stoff JS. Triple Therapy in Cadaveric Renal Transplantation: Role of Induction Cyclosporine and Targeted Levels to Avoid Rejection. *J Urol*, 153: 1805-1810, 1995.
6. Pedersen AR. Spurious Results in Therapeutic Drug Monitoring Research. *Therap Drug Monitor*, 24:775-784, 2002.

- Rousseau A, Monchaud C, Debord J, Vervier I, Estenne M, Thiry P, Marquet P. Bayesian Forecasting of Oral Cyclosporine Pharmacokinetics in Stable Lung Transplant Recipients with and without Cystic Fibrosis. *Therap Drug Monitor*, 25: 28-35. 2003.

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# MATT Meeting Calendar

**Lab Portal Jamboree: Powering Your Lab with Web Functionality**

February 27- 28, 2003, Miami Beach, FL. web site: <http://www.aacc.org>

**Society of Toxicology (SOT)**, March 9-13, Salt Lake City, UT. Contact: SOT 703-438-3115, website:

[www.toxexpo.com](http://www.toxexpo.com)

**Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy-Pittcon 2003**, March 9-14, Orlando, FL., Contact 412-825-3220, email: [pittconinfo@pittcon.org](mailto:pittconinfo@pittcon.org)

**Use of Flow Cytometry in Non-Human Species**, April 4, 2003 - East Hanover, NJ, Sponsored by AACC Animal Division and hosted by Novartis. web site: <http://www.aacc.org>

**35th Annual Oak Ridge Conference New Approaches to Diagnosing Neurological Diseases:Brainstorming for Clinical Laboratories**

April 10-11, 2003, Arlington, VA. web site: <http://www.aacc.org>

**Professional Practice in Clinical Chemistry: A Review & Update**

April 27 - May 1, 2003, Arlington, VA. web site: <http://www.aacc.org>

**MATT Annual Meeting**, May 8-9, 2003, East Lansing, MI. Contact: Fred House: 517-322-5536, or web site: <http://www.midwesttox.org>

**AACC 2003 Annual Meeting and Clinical Lab Expo**, July 20-24, 2003, Philadelphia, PA. Contact web site: <http://www.aacc.org>

**8<sup>th</sup> International Congress on Therapeutic Drug Monitoring and Clinical Toxicology**, September 7-11, 2003, Basel, Switzerland. Website: <http://ictdmct2003.ch/>

**American College of Clinical Pharmacology 32<sup>nd</sup> Annual Meeting**, September 21-23, Tampa, FL, Contact: Susan Ulrich email: [AACP1ssu@aol.com](mailto:AACP1ssu@aol.com)

**AACC San Diego Conference**, October 30 - November 1, 2003, Baltimore, MD. web site: <http://www.aacc.org>

**Society of Forensic Toxicologists Annual Meeting**, October 20-24, 2003, Portland, Oregon. Contact: Kent Johnson, 503-413-2069, website: <http://www.soft-tox.org>

**15<sup>th</sup> Annual Forensic Science Seminar**, sponsored by the Milwaukee County Medical Examiners' Office, October ?, 2003, Milwaukee, WI. Contact: Ms. Eileen Weller, 414-223-1207.





Presents MATT 2003  
**East Lansing, Michigan May 8-9, 2003**

### Registration Information

The meeting site is The Student union at Michigan State University. The basic meeting registration includes scientific sessions, posters and exhibits, program book, continental breakfast and luncheon Thursday and Friday and all coffee breaks. Registration is encouraged prior to April 15, 2003. Prices will be noted on the registration form. On-site registration will require a late fee.

### Hotel Registration and Transportation

Rooms have been blocked at the Kellogg Hotel and Conference Center at Michigan State University. Reservations for rooms should be made directly with the Kellogg Center. Room Rates are \$90.00 for a standard double and \$99.00 for a deluxe queen. Parking is available at the Kellogg Center Parking Garage. Call 1-800-875-5090 to reserve your room. For alternate lodging options, contact Fred House.

### Abstract Submission

MATT 2003 is pleased to offer the opportunity for poster presentations. We encourage subjects related to toxicology, either clinical or forensic. We will also consider general laboratory subjects such as quality control practices. This is an ideal opportunity to present for the first time. Do you have a great method that could benefit other members of the toxicology community? Please share it with us!

### Entertainment

There are a host of activities available on Campus and in the area. Miles of pathways wind around a beautiful campus and museums, fine arts entertainment, botanical gardens and golf are just a few of the amenities to be experienced.

For additional meeting information contact:

Fred House  
Phone: (517) 322-5536  
e-mail: [HouseF@michigan.gov](mailto:HouseF@michigan.gov)  
fax: (517) 322-5508

Laureen Marinetti  
e-mail: [LMarinetti@aol.com](mailto:LMarinetti@aol.com)



MATT 2003 Registration Form  
**Michigan State University Union**  
**East Lansing, Michigan - May 8-9, 2003**

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<b>Membership renewal for 2003</b>	\$20		\$ _____

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**MAIL TO:** Laureen Marinetti Questions or comments – MarinettiL@mcoho.org  
 Chief Toxicologist (937) 225-4156 ext. 2310  
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