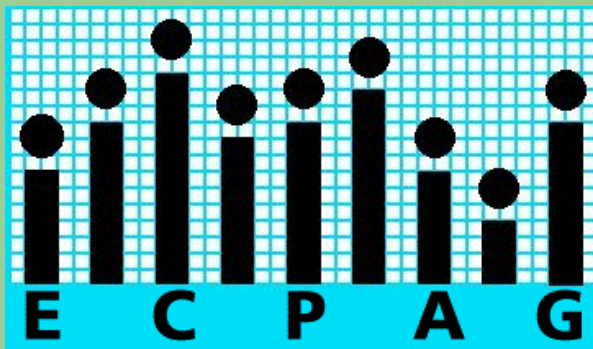# WELCOME to the 6th Annual East Coast Population Analysis Group Conference
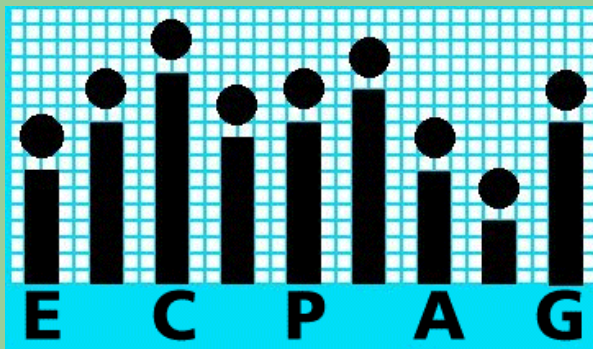
Rockville, MD

April 26 – 27, 2004
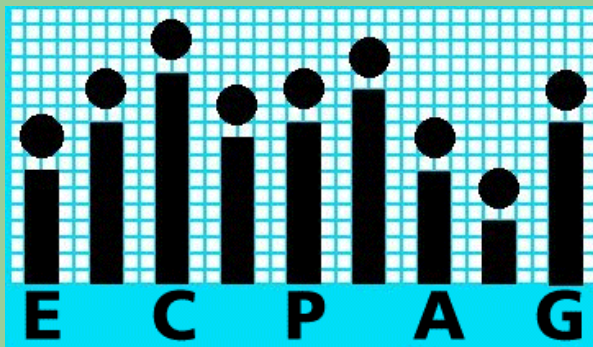
Themed Workshops: Validation Issues for Population PK/PD Models & Software Systems

Workshop Session I:

Model Qualification

E C P A G

Introduction to Workshop Session I: Content and Terms

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Overview of Session I

- Overview of Model Evaluation Methodologies – Marc Gastonguay

- Interactive Session: 4 case studies

- Selecting the Right Model Across Modeling Platforms – A Population PK/PD Perspective – Steve Duffull

- Open Discussion

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What Is A "Good" Model?

- A model is our "opinion" of the situation at one stage of the investigation – Draper & Smith, 1981
- "All models are wrong, but some are useful."
  – George Box
- The definition of "good" depends on the purpose of the model
  - It is possible for a model to be great for one purpose and completely inadequate for another
  - Do the model deficiencies have a noticeable effect on the substantive inferences made from the model?
    (ref: FDA Guidance for Industry, Population Pharmacokinetics 1999)

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Model Validation

- "… obtaining information about how well a population model describes a set of data (called the 'validation' or 'test' set), none of which was used to develop the model itself." (Stuart Beal e-mail to NMUser'sNet 2/1/94)
  - Evaluate the description in terms of both behavior and proposed application (FDA Guidance, Population PK)
- See how close model predictions are to validation data (predictive performance)
- Consider clinical vs. statistical satisfaction

Can A Model Be Validated?

- Consider the systems perspective (Diane will address in more detail later today …)
- Models do not exist in a vacuum
- A particular model is based on …
  - Data content and quality (study design, inherent data errors plus formatting errors and their implications)
  - Software (both NONMEM, front- and back-end applications, FORTRAN, etc.)
  - System it is run on (hardware, operating system, grid/cluster implementation, etc.)
  - People who run/develop it

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To Validate or Not To Validate …

- It's all about the intended use of the model
- Not all population models need to be validated
  - If the intention is to explain variability with no dosage adjustment consequence, then test for stability only
  - However, if there are drug labeling implications, then model validation is recommended and should be included/described in the protocol (FDA Guidance for Industry, Population PK)

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Model Checking

- Although the terms validation, verification, and qualification have very specific meanings in many fields, when it comes to population modeling, it seems there is model validation and …

- Model checking, model evaluation, model appropriateness testing, model stability testing, and many other names which may all have similar connotations indicating good practices for evaluating population models

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Relevancy: Putting Model Validation Into Context

- How important is validation of models in light of all of the other components of a system which also should be "validated"?

- Where do we hope to go with the possible application and implications of our models?
  - FDA's Exposure-Response Guidance puts E-R info at the heart of the determination of drug safety & efficacy
  - Population models are no longer only supplemental

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Workshop Learning Objectives

- Describe various approaches to model evaluation (using NONMEM and other software applications)

- Describe the circumstances under which particular approaches may be appropriate/inappropriate

- Describe and discuss some model selection techniques

- Illustrate through case studies various examples and considerations for model validation implementation