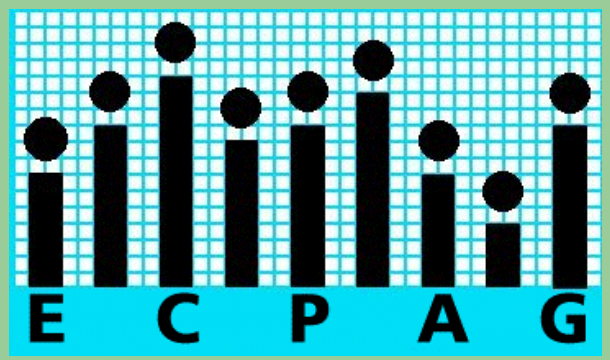
Documentation of Population Software Validation Efforts

Jill Fiedler-Kelly, M.S.
Cognigen Corporation



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A Regulatory Perspective

- FDA Guidance for Industry: Computerized Systems Used in Clinical Trials, 1999
  - "Software Validation means confirmation by examination *and provision of objective evidence* that software specifications conform to user needs and intended uses, and that the particular requirements implemented through the software can be consistently fulfilled."
  - Purchasers of off-the-shelf software should perform functional testing (e.g., by use of test data sets) and research known software limitations, problems and defect corrections.
  - Documentation to include spec's, test plans, and test results
  - Change control should be documented and re-validation performed based on risk

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A Regulatory Perspective (cont'd)

- FDA Guidance: General Principles of Software Validation
  - Applicable to software related to regulated medical devices and in part, in response to medical device recalls, of which 79% of those related to software (1992 – 1998) were caused by software defects introduced when changes were made to the software after initial production and distribution

A Regulatory Perspective (cont'd)

- 21 CFR Part 314.50 re: NDA Content & format
  - "(d) Each technical section is required to contain data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the application or …"
- 21 CFR Part 11
  - Off-the-shelf software should be validated for its intended use
- Quite possibly others too …

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SDLC Activities and Documentation of Validation Efforts

- A framework for monitoring and controlling software development projects
- Many different models exist
- Typical activities (for purchased software) may include:
  - Detailed Software Requirements Specification & Overall Plan
  - Vendor Implementation of Requirements, Design, Implementation & Testing
  - Installation & Acceptance Testing
  - Operation & Support
  - Maintenance
  - Retirement

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If It's Not Documented, It's Not Done

- Continuum of possibilities from bare minimum to very extensive effort
- In general, the documentation should match the effort and the effort should match the risk
- Documentation of the validation effort is the only proof you have that you've done it
  - It is the objective evidence

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Commercially Available Validation Testkits, e.g., WinNonlin/Mix

- Outlines the procedure to be completed
- Includes automated testing tools as well as relevant suggested SOPs, acceptance criteria and test plans, which can be modified
- Suggestions on documentation of validation efforts as well as event reporting, changes to the system, training
- Documentation to include: description of procedures, acceptance criteria, testing summary, SOPs, summary statement of validation

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Considerations for Documentation of NONMEM Validation Efforts

- No “validation kit”, so …
- Is it enough to run CONTROL3 – CONTROL7 successfully?
- A myriad of options and possibilities when it comes to population modeling in NONMEM
- Running the same problem in another package may or may not be possible, but hand-calculating is definitely not for most population problems

NONMEM Example – What is Enough, What is Too Much?

- Given the evolution of the use of population methods, the exposure-response guidance, and the potential for the use of population methods for E-R assessments impacting directly on evaluations of drug safety and efficacy …
- What is a reasonable validation effort and documentation of same for NONMEM?

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Example Validation Documentation for NONMEM

- Link to example documentation in PERSPECTIVE

Cost/Benefit Ratio

- Very time-consuming and expensive to do the first time
- Less so the next time when there is an upgrade or other change in the system, but there is a continuing cost, minimally maintenance
- Regulatory compliance
- Audit preparedness
- Should result in:
  - decreased failure rates
  - less risk from applications/models
- Consider the benefit to the customer and the implications of use

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Thank You

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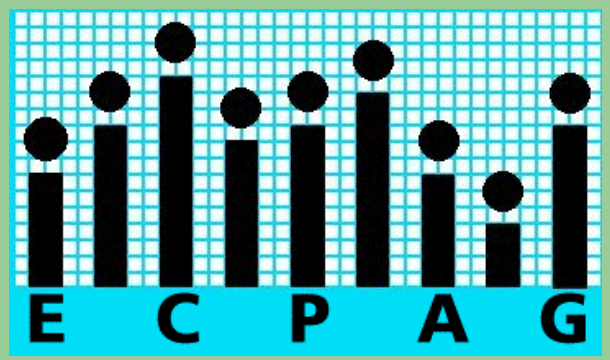
Cognigen Corporation



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Commercial Off the Shelf (COTS) Software Validation

Example of Documentation of Validation Activities for COTS Software

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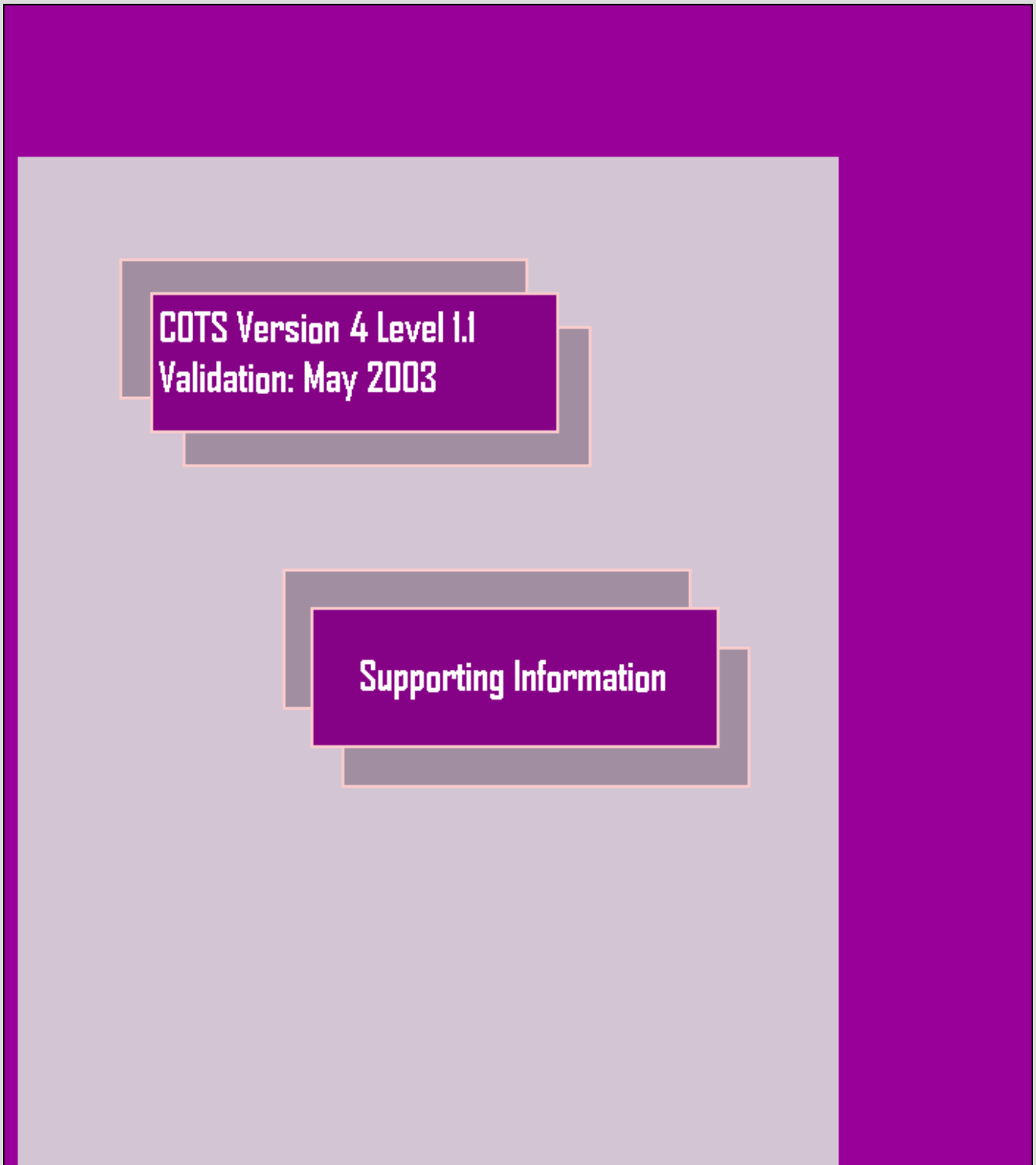
This sample map illustrates the use of **PERSPECTIVE Hypertext Data Analysis Mapping** software to document and organize a generic example of Commercial Off the Shelf (COTS) software validation processes and results in accordance with Cognigen's SOPs.



Page authored by Validation Specialist

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COTS Version 4 Level 1.1 Validation: May 2003

Documentation of Validation Activities for COTS

Specific information and documentation on the validation of COTS version 4 Level 1.1.