COMPUTER BASED TOOLS FOR THE QUALITY ASSURANCE AUDITOR

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ABSTRACT

For many QA sponsor and contract auditors, off-site audit activities occur at a client site in an office, in a conference room, or even in a livestock barn. Audit completeness, accuracy, efficiency, and independence are integral and critical objectives of job activities performed in locations outside your primary office. This poster discusses computer-based tools that you can carry to the audit site to help meet the above goals. For this poster, we assume that you as the auditor have a laptop computer that is used on the road and that internet access is not always possible. The tools presented in this poster are primarily directed toward GLP audits, but similar models may be used for GCP and/or GMP applications. Six general types of reference tools are discussed (1) Government regulations and guidance documents, (2) SOPs and Checklists, (3) Other relevant articles, (4) Computer and PDA Software, (5) Databases and tables, and (6) Spreadsheet based templates. For each area we discuss why we carry the information, sources of materials, applications and audit examples.

REGULATIONS & GUIDANCE DOCUMENTS

Downloaded Word documents of regulations, guidelines, and guidance documents

Why: Word / html documents can be saved to your computer to be available for reference during audits. You can search for key words or topics by using the key sequence "Ctrl + F" or sections of the text can be copied and pasted into an audit report or training presentation.

Source: Regulatory websites.

Example: **Guidance for Industry: Bioanalytical Method Validation**

Source: http://www.fda.gov/cder/guidance/4252fnl.htm

Audit Applications: This document can be cited as primary reference when reviewing validation protocols and SOPs. More typically, documents are used to develop **CHECKLISTS** or **SPREADSHEETS** (right).

Other Examples:

21 CFR 58 source: http://www.fda.gov Select Code of Federal Regulations under Reference Room, Select 58 for "Part.Section"

BIMO 7348.808; GLP Inspections source: http://www.fda.gov/ora/compliance_ref/bimo/7348_08/default.htm

CVM No. 85; VICH GL9; Good Clinical Practice source: http://www.fda.gov/cvm/guidance/guide85.doc

ICH E6; Good Clinical Practice source: http://www.ich.org Select Guidelines under Publications, Select E (Efficacy topics), Select E6 (PDF version available only)

ELECTRONIC SOPs

Current electronic SOPs

Why: Technical details of SOPs will be available for reference during your audit.

Source: If available electronically, download/copy your (or your client's) current SOPs applicable to your audit tasks.

Audit Applications: In addition, task lists can be used to develop other audit tools such as **CHECKLISTS** or **SPREADSHEETS** (right).

HARDWARE

* Laptop	* USB number keypad	* USB Mouse	* CD Drive
* PDA	* USB External (flash) drive	* DSL line and adaptor	* Blank CDs

* **Current Contact Information:**
Manager, Quality Assurance – Bioanalysis
MDS Pharma Services
621 Rose Street; Lincoln, NE 68502
Office: (402) 437-6317
Cell: (870) 926-3182
Fax: (402) 467-7598
E-mail: richard.vanderpool@mdsinc.com
Website: http://mdsps.com

CHECKLISTS & SPREADSHEETS

Checklists:

Electronic tools such as regulatory documents, internal SOPS, and study protocols can be transformed into electronic checklists used for reviewing data and records during your audit. Ideally, a checklist is a bullet list that can be used for documenting audit tasks, if necessary.

Example: Items on a checklist listing critical elements a reviewer expects in a method validation protocol or report:

	Yes	No
• Regression model and residuals		
• Intra- and Inter-batch precision and accuracy		
• Extraction recovery		
• Dilution QC		
• Interfering substances		
• Bench top stability		
• Room temperature extract stability		
• Refrigerated extract stability		
• Freezer stability		
• Freeze/thaw stability		
• Ruggedness - another system		
• Ruggedness - another analyst		

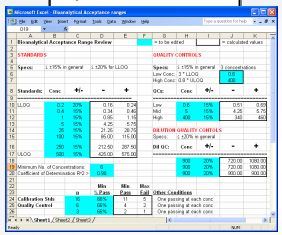
Comments: _____

Other checklist examples:
Study Protocol
Final Report
Analytical/Central lab facility
Animal facility
Study management (sponsor monitoring)
Contributing Scientist Report
Bioanalytical/TK/PK Report
Clinical Investigator Site
Clinical trial data management

Spreadsheets:

Spreadsheets can be developed from the study protocol, analytical method, or SOPs to minimize audit time once you are on site.

Example: Protocol-specific Excel spreadsheet developed to calculate upper and lower passing concentration limits for standards and QCs for an analytical method. Inputs (blue backgrounds) are taken from the method validation and are used to calculated values in analytical runs.



REFERENCE SOFTWARE

English Dictionary and Thesaurus:

Source: Free download for basic software; affordable upgrades at http://wordweb.info/free/

Application: Tool for writing audit reports and preparing training presentations/handouts.

Medical Dictionary:

Source: http://www.Franklin.com, many others for laptop; http://www.beiks.com/palmzonebg/Lexicons/Medical.htm for PDA

Physician's Desk Reference (PDR):

Source: Card for PDA and/or CD-ROM for laptop
www.Franklin.com www.micromedex.com/products/pdrlibrary

Application: Reviewing concomitant medications

Glossaries:

Source: Developed in-house or obtained from professional organizations
Statistics
Information Technology
Toxicokinetic/Pharmacokinetic
Abbreviations

APPLICATION SOFTWARE

MS Office Professional: Equation Editor and Solver

Why: Equation Editor (MS Word); Solver (Excel): In many instances, limited or default software installations omit these two utilities. With Microsoft Office Professional, Equation Editor (MS Word) and Solver (Excel) may be useful for developing spreadsheet-based templates.

Source: The Equation Editor is used in MS Word as "Microsoft Equation 3.0" and can be found via the tool bar under "< Insert, Object…, Create New, Microsoft Equation 3.0". This opens a text box and the equation tool bar allowing the generation of equations such as:

$$x = \frac{-b \pm \sqrt{b^2 - 4a(c-y)}}{2a}$$

Source: Solver is an Excel "Add-In" and is found in the tool bar via <Tools, Solver…>. If Solver is not in the menu, select <Tools, Add-Ins…>. In the Add-Ins Dialog box check "Solver Add-in" and "OK". This will install Solver and add Solver to the Tools menu. This addition may require the Microsoft Office installation disk. With a data set, Solver can be used to calculate numeric values for a, b, and c in the quadratic equation shown above. See http://www.biotechnicalservices.com/ - under "Helpful Downloads" you will find a section for Presentation Downloads which include 1) Excel Solver Templates 2) QA 2005 Expanded Poster (discussed the templates) 3) SAS 1st Order Output 4) SAS 2nd Order Output (SAS reference data for templates)

Application: When reviewing spreadsheets, templates, or calculated results, errors may be noted in equations. The equation editor tool allows the auditor to recreate and/or duplicate the equation in the report (see example above). The alternative, x = -b +/- (b^2-4a(c-y))^0.5/2a, is less satisfactory. In bioanalytical method templates, we input known standard concentrations and instrument derived peak areas for the standards, then use Solver to recalculate a, b or a, b, c in equations used in LC/MS/MS calibration curves.

Molecular Weight Calculator Software

Why: We have found instances where the report listed the structure and/or formula for the salt while the molecular weight was for the free base.

Source: http://jorg.chem.unc.edu/personal/monroe/mwtwin.html
Freeware designed by Bill Monroe for Windows 9x/NT/00/ME/XP. Download file "mwt6_37.zip" for Version 6.37 (3.1 MB, December 26, 2004). The software calculates the molecular weight for a given formula (Partial structural or Hill).

Application: Method validations include the chemical structure and formula weight for the standard, internal standard, and/or analyte. While the standard may be supplied in the salt form, the method measures the free base. Bioanalytical calculations include the molecular weight ratios of the free base to salt.

The software allows the auditor to verify that the molecular weight listed in the report matches the reported structure or formula. Calculated examples for:
Formula 1 - Morphine (freebase form)
Formula 2 - Morphine sulfate
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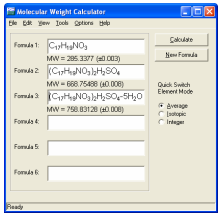

Daycount software

Why: Determining study day for complex studies can be time consuming. This software will determine the study day for any dates you enter.

Source: Available for PDA at http://www.keyfocus.net/palm/

REFERENCE TABLES

Conversion Table:
Why: Unit conversions, solution preparation calculations, other chemistry calculations
Source: ProKon software - description at http://www.showmepro.com/prodesc.htm Version 10 costs $24.95 (4-12-2006)
Application: Internet tools for scientific unit conversion may not always be accessible in the field. Inexpensive conversion tables can be downloaded to your laptop for reference. Do some research to find one that works best for your audit tasks. ProKon appears to be one of the best.

Reference Ranges for Clinical Pathology parameters:
Why: Reviewing clinical pathology data for various species.
Source: http://www.diaglab.vet.cornell.edu/clinpath/reference/
Application: Numerous web sites offer reference ranges for typical laboratory safety screens. These reference ranges can be copied and pasted into a Word document on your computer. Use these ranges with caution - they are specific to individual laboratories and testing instruments. In addition, these tables are often copyright protected. Do not distribute.

SPREADSHEET-BASED TEMPLATES

Example:
Pharmacokinetics Area Under the Curve (AUC) Calculations

Why: Pharmacokinetic studies are required by 21 CFR Part 320.21(g)(1) & 25(g)(3) and AUC is specifically addressed in the Center for Veterinary Medicine Guidance for Industry Bioequivalency Guidance #35.

Source: M. Gibaldi, D. Perrier. Pharmacokinetics, 2nd Ed.; Marcel Dekker, New York, 1982 (Appendix D) (Out of print, but used texts are available)

AUC Equations:

Linear Trapezoidal Rule $$AUC = \sum \left(\frac{(t_2 - t_1)}{2} * (C_1 + C_2) \right)$$

Log Trapezoidal Rule $$AUC = \sum \left(\frac{(C_1 - C_2) * (t_2 - t_1)}{(\ln C_1 - \ln C_2)} \right)$$

Application:

- Template for AUC calculations is used for the verification of reported AUC values.
- Reported Sum AUC calculated from individual AUC values – e.g. 4 & 8 hr pair.
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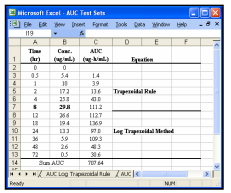

Other Spreadsheet-based Templates

Quadratic Equation
Regression fitting (weighted, linear, quadratic)
Random Number template
Radiation calculations
Geometric Mean Calculation

OTHER SUGGESTIONS

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____

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CVM No. 85; VICH GL9; Good Clinical Practice source: http://www.fda.gov/cvm/guidance/guide85.doc

ICH E6; Good Clinical Practice source: http://www.ich.org Select Guidelines under Publications, Select E (Efficacy topics), Select E6 (PDF version available only)

ELECTRONIC SOPS

Current electronic SOPs

Why: Technical details of SOPs will be available for reference during your audit.

Source: If available electronically, download/copy your (or your client's) current SOPs applicable to your audit tasks.

Audit Applications: In addition, task lists can be used to develop other audit tools such as **CHECKLISTS** or **SPREADSHEETS** (right).

HARDWARE

Laptop; USB number keypad; USB Mouse; CD Drive; PDA; USB External (flash) drive; DSL line and adaptor; Blank CDs

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Dilution QC		
Interfering substances		
Bench top stability		
Room temperature extract stability		
Refrigerated extract stability		
Freezer stability		
Freeze/thaw stability		
Ruggedness - another system		
Ruggedness - another analyst		

Comments: _____

Other checklist examples:

Study Protocol
Final Report
Analytical/Central lab facility
Animal facility
Study management (sponsor monitoring)
Contributing Scientist Report
Bioanalytical/TK/PK Report
Clinical Investigator Site
Clinical trial data management

Spreadsheets:

Spreadsheets can be developed from the study protocol, analytical method, or SOPs to minimize audit time once you are on site.

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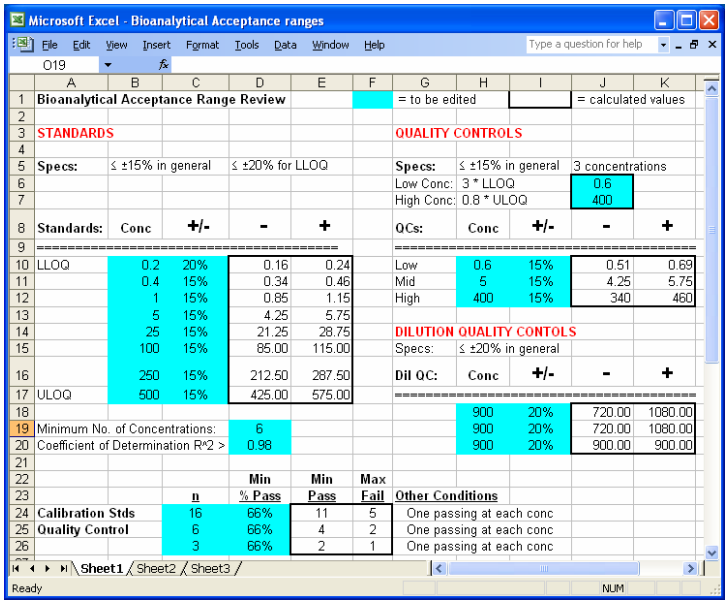

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www.Franklin.com
www.micromedex.com/products/pdrlibrary
Application: Reviewing concomitant medications

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Source: Developed in-house or obtained from professional organizations
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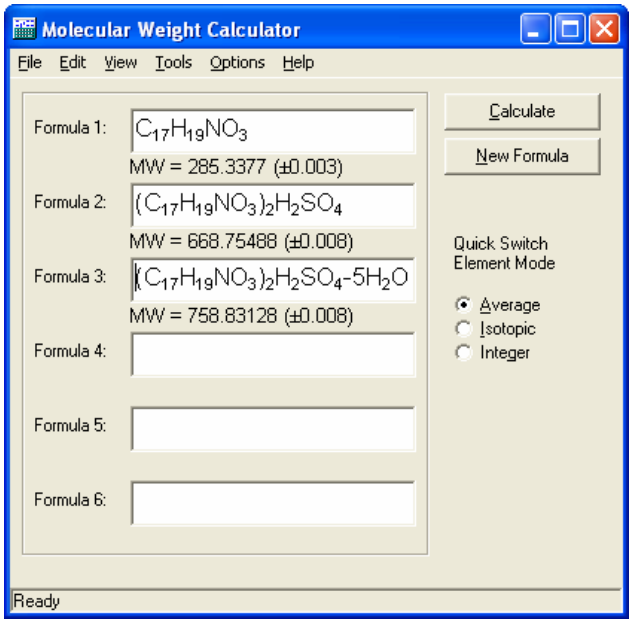

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REFERENCE TABLES

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Why: Unit conversions, solution preparation calculations, other chemistry calculations

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Application: Internet tools for scientific unit conversion may not always be accessible in the field. Inexpensive conversion tables can be downloaded to your laptop for reference. Do some research to find one that works best for your audit tasks. ProKon appears to be one of the best.

Reference Ranges for Clinical Pathology parameters:

Why: Reviewing clinical pathology data for various species.

Source: http://www.diaglab.vet.cornell.edu/clinpath/reference/

Application: Numerous web sites offer reference ranges for typical laboratory safety screens. These reference ranges can be copied and pasted into a Word document on your computer. Use these ranges with caution - they are specific to individual laboratories and testing instruments. In addition, these tables are often copyright protected. Do not distribute.

SPREADSHEET–BASED TEMPLATES

Example: Pharmacokinetics Area Under the Curve (AUC) Calculations

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AUC Equations: Linear Trapezoidal Rule

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Log Trapezoidal Rule

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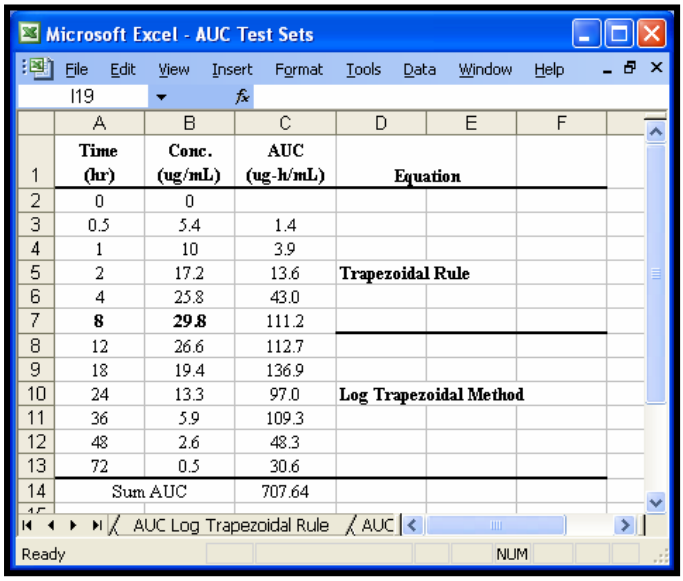

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OTHER SUGGESTIONS

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Manager, Quality Assurance – Bioanalysis
MDS Pharma Services
621 Rose Street; Lincoln, NE 68502
Office: (402) 437-6317
Cell: (870) 926-3182
Fax: (402) 467-7598
E-mail: richard.vanderpool@mdsinc.com
Website: http://mdsps.com