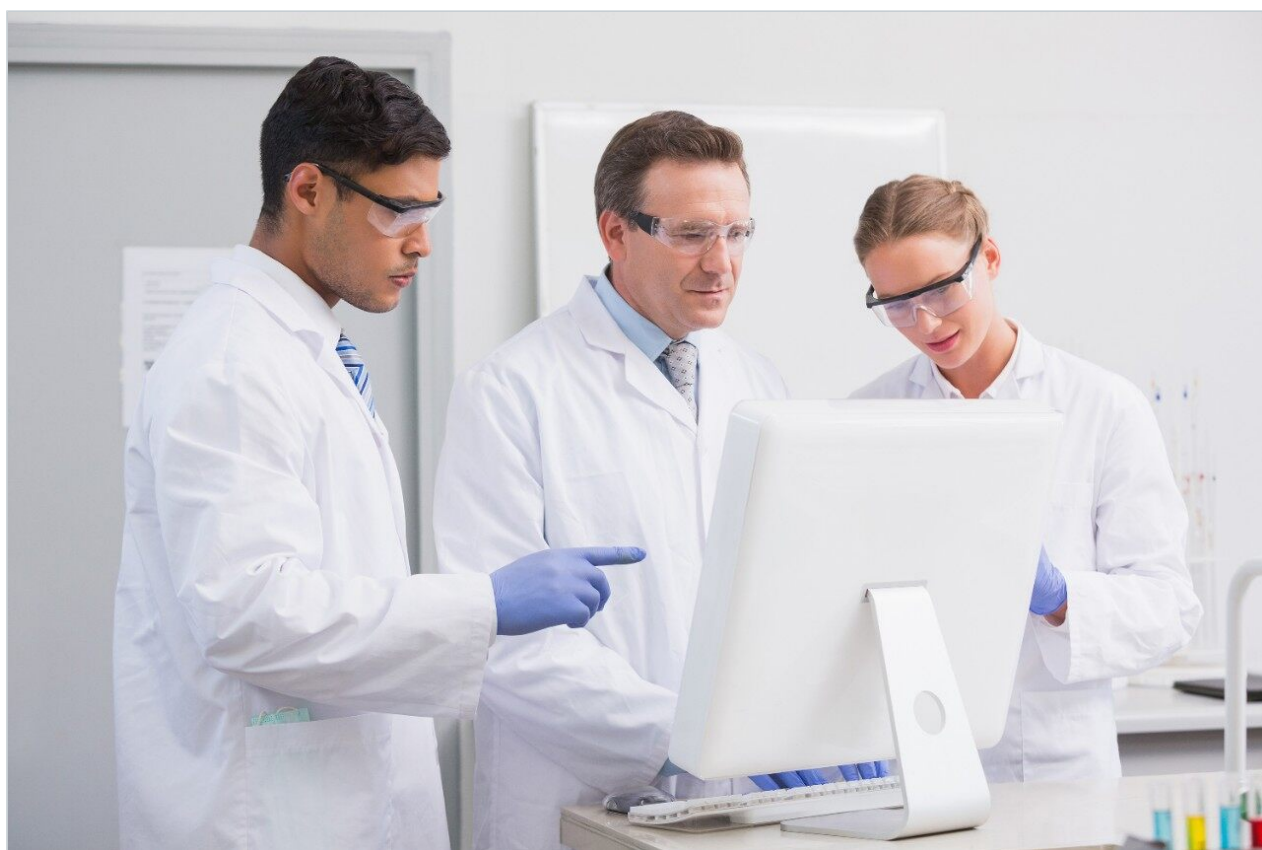


应用纪要

GxP Spreadsheets Encapsulated in a Compliant-Ready Solution

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Waters Corporation



Abstract

This application note will demonstrate how a Microsoft Excel spreadsheet document functions in a GxP Laboratory by implementing NuGenesis SDMS.

Introduction

The first commercially available electronic spreadsheet was released in 1979.¹ During the 1980s, the financial and accounting industries rapidly implemented electronic spreadsheets and adoption quickly spread to other arenas, including the sciences. Today, electronic spreadsheets are widely used in scientific laboratories to provide experimental result interpretations, such as plotting data into charts, performing simple-to-complex calculations, and serving as simple databases.

Laboratories adhering to regulations such as 21 CFR Part 11, Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP) in compliance with 21 CFR Parts 58 and 211, seek to ensure that electronic records, including electronic spreadsheets are trustworthy, reliable, and equivalent to paper records. Built-in safeguards that ensure data authenticity such as electronic signatures, audit trails, and date and time stamps are not provided with electronic spreadsheets such as Microsoft Excel. U.S. regulators have issued warning letters citing insufficient controls for spreadsheets that are used in regulated environments.^{2,3,4} In order to utilize electronic spreadsheets in the GxP environment, spreadsheets such as Excel need additional controls. Electronic Laboratory Notebooks (ELN), and Scientific Data Management Systems (SDMS) are software applications that provide a mechanism to increase spreadsheet control.

Waters NuGenesis SDMS acts as a data repository for file data and printed electronic records as a core feature. Added functionality of NuGenesis SDMS includes SDMS Vision Publisher, a report and authoring tool, and SDMS Intelligent Procedure Manager, a GxP workflow documentation tool. Both Vision Publisher and Intelligent Procedure Manager can serve as a compliant ready shell for maintaining the authenticity of Microsoft Excel electronic documents (Figure 1). This compliant-ready functionality makes the functionality of Microsoft Excel spreadsheets accessible to analysts working in GxP laboratories by providing the necessary safeguards for using electronic documents in GxP environments.

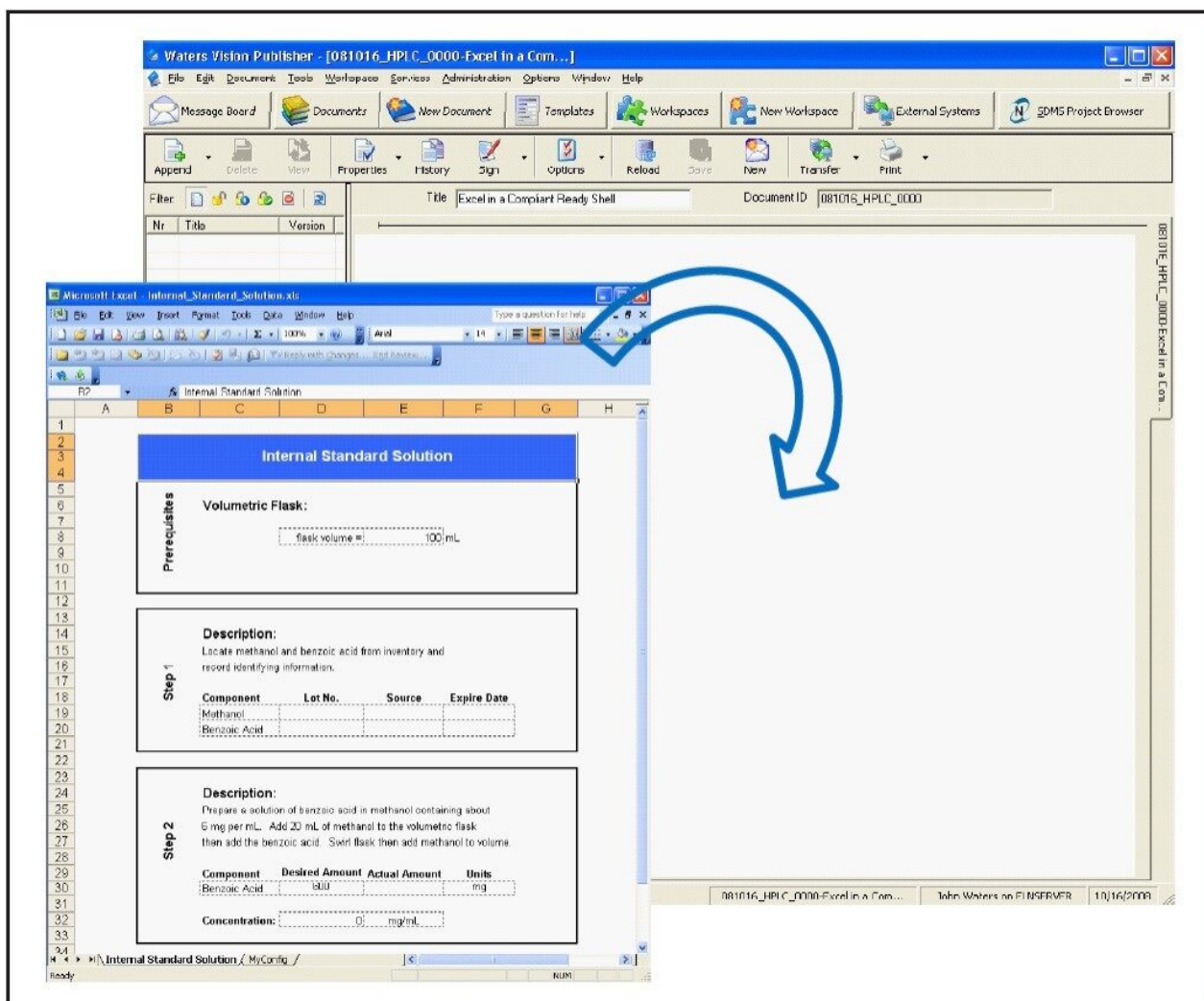


Figure 1. Microsoft Excel embedded within the compliant-ready shell of SDMS Vision Publisher.

This application note will demonstrate how a Microsoft Excel spreadsheet document functions in a GxP Laboratory by implementing NuGenesis SDMS.

Results and Discussion

Preparing an Excel Worksheet

Extensive practice of Standard Operation Procedures (SOPs) ensures quality and consistency during laboratory procedures in the regulated laboratory. Figure 2 illustrates an electronic form

implemented by using Microsoft Excel. The form contains data input fields and a formula for determining solution concentration. Formula accuracy for the calculation may be verified manually or by comparison with a validated mathematical software package.

The screenshot shows a Microsoft Excel spreadsheet titled "Internal Standard Solution.xls". The form is structured as follows:

	A	B	C	D	E	F	G	H
1								
2		Internal Standard Solution						
3								
4								
5								
6	Prerequisites	Volumetric Flask:						
7								
8		flask volume = 100 mL						
9								
10								
11								
12	Step 1	Description:						
13		Locate methanol and benzoic acid from inventory and record identifying information.						
14								
15								
16								
17								
18		Component	Lot No.	Source	Expire Date			
19		Methanol						
20		Benzoic Acid						
21								
22								
23	Step 2	Description:						
24		Prepare a solution of benzoic acid in methanol containing about 6 mg per mL. Add 20 mL of methanol to the volumetric flask then add the benzoic acid. Swirl flask then add methanol to volume.						
25								
26								
27								
28								
29		Component	Desired Amount	Actual Amount	Units			
30	Benzoic Acid	600		mg				
31								
32	Concentration:	0	mg/mL					
33								
34								

The bottom of the spreadsheet shows the "Internal Standard Solution" sheet tab and the status bar with "Ready" and "NUM" indicators.

Figure 2. Form created in Microsoft Excel including a concentration calculation utilizing a verified equation.

Embedding and Using Excel

Once the spreadsheet calculations have been qualified, the spreadsheet still lacks version control and unauthorized modifications may compromise confidence in experimental results. Incorporating an Excel form into the compliant-ready framework of the Vision Publisher tool enables the integration of 21 CFR Part 11 requirements such as audit trails and version control. A relational database such as Oracle provides data traceability to support the implementation of 21 CFR Part 11 requirements. Embedding a spreadsheet within Vision Publisher begins with the system login (Figure 3). Adding an Excel form requires a user to login with administrative privileges. Object Linking and Embedding (OLE) technology^{5,6} provide the connectivity to incorporate an Excel form into Vision Publisher. The file browser dialog window allows the administrator to locate the Excel form on the system (Figure 4) and assign it to SDMS Vision Publisher (Figure 5). Once the form resides within SDMS Vision Publisher, the administrator can assign access levels to the document. Verified formulae and input fields can be password protected and finally SDMS Vision Publisher tracks, via an audit trail (Figure 6), input made by the user.

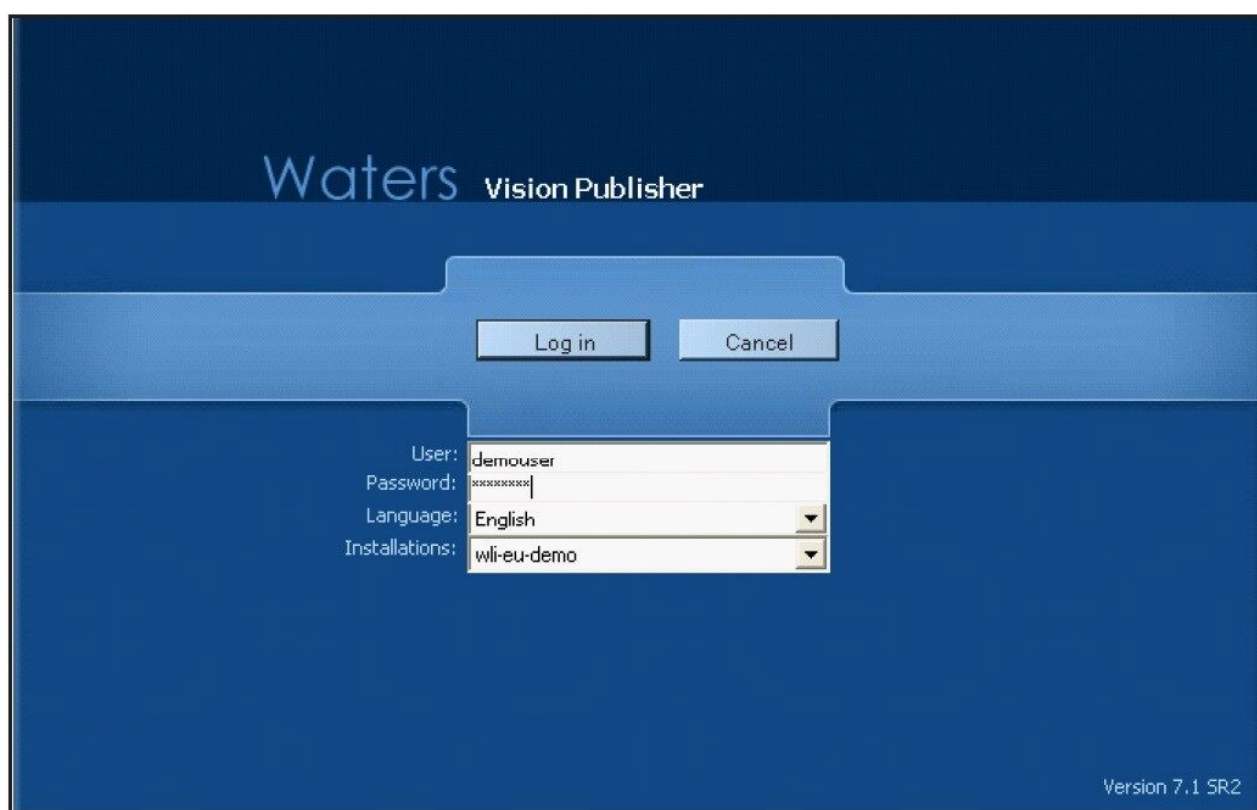


Figure 3. Electronic login to SMDS Vision Publisher. Analyst supplies unique user name and password.



Figure 4. Microsoft Excel form inserted into SDMS Vision Publisher as an OLE object. Form selected for inclusion with a file browser dialog window.

Waters Vision Publisher - [Section Management]

File Document Tools Workspace Services Administration Options Window Help

Message Board Documents New Document Templates Workspaces New Workspace External Systems SDMS Project Browser

Show All

Active Demo
Analytical Data
Chromatogram
Spectrum
Chemistry
Reactions
Reactions
Structures
Structures
CoA
DMPK
DMPK-Solutions
Documents
General Forms
Blue Skies Head
Counter Form
Equipment List
Internal Standard
Reagent List
SDS Balance Ti
Std Preparation
Graphics
Grimm
HPLC Forms
Instruments
LIMS
MV Forms
Mass Spec Forms
Math & Stat
Office
Excel
PowerPoint
Visio
Word
rs1
PharmaFun
Reports
SDK
Copper Determination
Dissolution
Equipment
Export
LIMS
Operating Parameters
Preparation of Samples
Project Info

Find Clear Save New Document Section New Workspace Section Delete Section(s) Attach Icon Hide Filter

Filter: N/A Show Query

Icon	Section	Description	Category	Type
	Intermediate Report		Reports	Workspace
	Internal Standard Solution		General Forms	Document

Object Type Metadata Access Renditions

Insert Object Type Delete Object Type

Internal Standard Solution

Prerequisites

Volumetric Flask:

flask volume = 100 mL

Step 1

Description:
Locate methanol and benzoic acid from inventory and record identifying information.

Component	Lot No.	Source	Expire Date
Methanol			
Benzoic Acid			

Step 2

Description:
Prepare a solution of benzoic acid in methanol containing about 6 mg per mL. Add 20 mL of methanol to the volumetric flask then add the benzoic acid. Swirl flask then add methanol to volume.

Component	Desired Amount	Actual Amount	Units
Benzoic Acid	600		mg

Section Management John Waters on ELNSERVER 10/16/2008

Figure 5. Microsoft Excel form added to SDMS Vision Publisher and available as a section in a SDMS Vision Publisher electronic document.

Document - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Home Search Favorites

Address C:\Documents and Settings\demouser\Application Data\Waters\Waters Vision Publisher\7.1.0.3\AuditTrail\33bbf54a-193a-4307-ad18-46f4 Go

Links NuGenesis Remote Server Console NuGenesis SDMS Audit Trail Viewer NuGenesis VISION

Ready Shell Compliant Ready Shell Waters

Document Sections

Internal Standard Solution Section

Section Title	Internal Standard Solution
Type	Internal Standard Solution
Position	1
Created on	16.10.2008 14:28:28 by Jim Waters
Author	Jim Waters
Modified on	16.10.2008 14:28:28 by Jim Waters

Modifications

Title	Position	Modified on
Internal Standard Solution	1	16.10.2008 14:28:28 by Jim Waters

Versions

Version Number	Version Type	Reason	Modified on	Modification
1	M		16.10.2008 14:28:28 by Jim Waters	Created
1	M		16.10.2008 14:32:45 by Jim Waters	Created
1	M		16.10.2008 14:33:32 by Jim Waters	Created

Section Metadata

Name	Type	Value	Required	Unit	Modified on	Modification
Form Control	String		<input type="checkbox"/>		16.10.2008 14:28:30 by Jim Waters	Created
Form Control Test	String		<input type="checkbox"/>		16.10.2008 14:28:31 by Jim Waters	Created

Document Signatures

Cycle	Signer	Action	Date/Time	Reason
1	Jim Waters	Release	16.10.2008 14:39	
1	Jim Waters	Approved	16.10.2008 14:42	OK

*All time data are displayed in UTC format.
Report created on 16.10.2008 14:42

Done My Computer

Figure 6. Modifications and signatures applied to Excel form tracked in the Audit Trail.

For the analyst, the spreadsheet functions normally with the exception that they can only provide input into designated fields and cannot modify the form or equations. Electronic signatures are available to the analyst and are initiated by releasing the document for review. The signature process requires a unique login and password combination as well as a signature reason (Figure 7). After the analyst applies their electronic signature, a notification for review and signature is automatically routed to a manager or supervisor. Up to 3 signatories may be configured for review

and signoff.

The screenshot shows a Windows-style dialog box titled "Approve: 081016_HPLC_0000 Excel in a Compliant Ready Shell". The dialog contains the following elements:

- Document Information:** Document: 081016_HPLC_0000 Status: Released; Title: Excel in a Compliant Ready Shell; Created by Jim Waters at 10/16/2008 10:16:36; Released by Jim Waters at 10/16/2008 10:39:37.
- Signature Section:** Labeled "Signature", it includes a "Reason:" dropdown menu. The dropdown is open, showing options: "Not OK", "OK", "Rejected", "Verified", and "Witnessed". Below the dropdown is a large text area for a signature.
- User ID:** A text field containing "Jim Waters".
- Password:** A text field with masked characters "xxxxxxx".
- Buttons:** At the bottom, there are three buttons: "Approve" (with a checkmark icon), "Reject" (with a red circle icon), and "Cancel".

Figure 7. Electronic signature applied to the completed document including reason for signature. Request for additional review and approval routed via electronic signature functionality.

Conclusion

Microsoft Excel is a versatile and powerful tool for performing laboratory calculations and plotting data, but does not provide a mechanism to adhere to regulations and guidances, such as 21 CFR Part 11 and Annex 11, for authentic and secure records. Incorporating Excel spreadsheets inside a compliant-ready shell like SDMS Vision Publisher enables regulated laboratories to utilize Excel while adhering to GxP regulations for authentic and traceable records.

Storing Excel content inside a compliant-ready shell like SDMS Vision Publisher can improve data record quality and reduce the quality operation cycle times for returning QC results. Quality assurance efforts benefit due to decreased record review times since records are housed centrally with complete audit trails. Greater efficiency and productivity result in shipping products faster and maximizing available resources.

References

1. Roeding, C. R.; Purkert, G.; Kindner, S.K.; Muller, R.; and Hoch, D. J. “Secrets of Software Success: Management Insights from 100 Software Firms Around the World” , ISBN 1578511054 (1999).
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 3. FDA Warning Letter; December 23, 2003; “cGMP Requirements of the Quality System Regulations/Adulterated” ; Center for Devices and Radiological Health.
 4. FDA Warning Letter; May 17, 2007; “CGMP Requirements for Medical Devices/Quality System Regulation” ; Los Angeles District Office.
 5. https://en.wikipedia.org/wiki/Object_Linking_and_Embedding <https://en.wikipedia.org/wiki/Object_Linking_and_Embedding>
 6. <http://support.microsoft.com/kb/86008> <<http://support.microsoft.com/kb/86008>>
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720002803, November 2008

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