

Paper 116-27

Using SAS[®] ODS to Enhance Clinical Data Summaries: Meeting eSub Guidelines

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ABSTRACT

SAS programmers in the pharmaceuticals industry are aware that the Food and Drug Administration (FDA) has raised the bar for presentation of summary tables and listings used as part of electronic submissions (eSub). Guidelines for font selection, font size, and margins have made traditional text file output somewhat more challenging to work with.

Fortunately for us, the new guidelines have coincided with the SAS Institute's implementation of the Output Delivery System (ODS), which provides the ability to both greatly enhance the appearance of tabular output and to meet the FDA's eSub guidelines. This presentation will provide an introduction to use of ODS in generating tabular reports using ODS (to RTF and PDF destinations) with a focus on the eSub guidelines and the advantages of using ODS over listing-mode output.

INTRODUCTION

FDA guidelines for eSub compliant reports place a new set of demands on SAS programmers generating study report tables, one of the most common applications of SAS in the industry. The page layout requirements and font sizing are considerably more demanding than what has commonly been used in the past, placing limitations on how much information can be 'cramped' into a single page.

At the same time companies are eager to implement ODS-style reporting both for in text tables and for study report appendices. This presentation describes the fundamental requirements for generating eSub compliant reporting and will demonstrate programming techniques and features of ODS in both RTF and PDF, to allow programmers to meet these requirements. We also discuss how ODS can enhance the visual quality and readability of reports, and the ultimate benefit to companies of making their reports more 'reviewer friendly'.

The technical focus of this paper is working with SAS Proc Report to generate tables, emphasizing the process of adapting code for use with ODS.

ESUB GUIDELINES FOR STATISTICAL TABLES

FDA Electronic Submission Guidelines (1) specify the following recommended standards for the appearance of statistical tables. Among these are included

- Font size as close to 12 as possible
- Paper size 8.5 x 11 inches
- Margins at least 1 inch on all sides
- Use only True Type or Adobe Type 1 fonts
- Limit the number of fonts in each document
- **Embed all fonts in the PDF file**

An unofficial rule of thumb, based on experiences with past submissions, is that a PDF document displayed at 100% on a 15 inch monitor should be easily readable, and when displayed at 200% should not display pixels. Past experience has shown that use of font sizes smaller than 8 will not be well received.

Based upon the unofficial rule, when producing listings and tables, we are limited to a SAS output file line size of about 140 characters maximum. These files can then be converted into documents with fonts of 8 point. This is the outer limit of acceptability, and in many cases can impede our ability to present the data as we like. Preparing tables for electronic submissions in a manner that exceeds minimum established guidelines is a challenge. If the goal is to produce a more readable table, listing mode output is a limiting factor. ODS output, especially output to an RTF file, can help us to fit data more cleanly into tables.

A TRADITIONAL LISTING MODE PROGRAM AND TABLE

A conventional listing mode vital signs table with four treatment groups and a combined treatment column might look something like that in Figure 1. This table was produced using Proc Report. When converted into a document using a SAS Monospace 8 pt. font, the readability of the table is at the limit of acceptability. If we had longer treatment group labels, longer parameter names or additional groups to present it would be difficult to display the table without compromising readability.

Parameter	Visit	Statistic	Dose Group				Combined Treatment Groups
			Placebo	100 mg Test Drug A	200 mg Test Drug A	400 mg Test Drug A	
Diastolic BP (mmHg)	2	N	8	7	16	8	39
		Mean	60.50	59.43	56.38	60.50	58.62
		Min	48.0	42.0	48.0	48.0	42.0
		Max	68.0	68.0	66.0	68.0	68.0
		StdErr	2.2	3.1	1.3	2.2	1.0
	6	N	8	7	16	8	39
		Mean	61.00	58.86	57.75	61.00	59.28
		Min	48.0	52.0	48.0	48.0	48.0
		Max	74.0	64.0	74.0	74.0	74.0
		StdErr	2.7	1.9	1.6	2.7	1.1
Systolic BP (mmHg)	2	N	8	7	16	8	39
		Mean	89.00	87.71	89.25	89.00	88.87
		Min	68.0	68.0	64.0	68.0	64.0
		Max	102.0	98.0	110.0	102.0	110.0
		StdErr	3.6	3.7	3.1	3.6	1.7
(etc..)							

Figure 1 – Vital Signs Table in Listing Mode

			Dose Group				
			Placebo	100 mg Test Drug A	200 mg Test Drug A	400 mg Test Drug A	Combined Treatment Groups
Parameter	Visit	Statistic					
Diastolic BP (mmHg)	2	N	8.0	7.0	16.0	8.0	39.0
		Mean	60.50	59.43	56.38	60.50	58.62
		Min	48.0	42.0	48.0	48.0	42.0
		Max	68.0	68.0	66.0	68.0	68.0
		StdErr	2.20	3.11	1.31	2.20	1.01
	6	N	8.0	7.0	16.0	8.0	39.0
		Mean	61.00	58.86	57.75	61.00	59.28
		Min	48.0	52.0	48.0	48.0	48.0
		Max	74.0	64.0	74.0	74.0	74.0
		StdErr	2.67	1.94	1.58	2.67	1.05
Systolic BP (mmHg)	2	N	8.0	7.0	16.0	8.0	39.0
		Mean	89.00	87.71	89.25	89.00	88.87
		Min	68.0	68.0	64.0	68.0	64.0
		Max	102.0	98.0	110.0	102.0	110.0
		StdErr	3.59	3.74	3.14	3.59	1.72

Figure 2 – Vital Signs Table using ODS RTF

USING ODS RTF

Using the same code and a customized ODS style we can generate the table shown in Figure 2. The ODS Style determines the fonts, colors page margins, etc. that are applied to the RTF file. Using the RTF style that is the default for the ODS RTF statement, and making changes as desired is a fairly straightforward process, once one has identified which style elements control the critical display components of the table.

Modifying the code to generate the RTF Table in Figure 2 requires the following two steps.

1. create a custom style specifying the borders, colors and fonts to be used
2. add ODS statements to open and close the RTF file, invoking the custom style

ADVANTAGES OF ODS RTF

The appearance of tables with relatively large quantities of data is enhanced through the use of more legible proportional fonts, use of color, and division of tables by lines (for text output Proc Report has a 'box' option that will draw lines around table cells, but it is limited in functionality.) Proportional fonts and lines dividing the table into cells allow data to be displayed in a tighter space without compromising readability. This allows us to fit more data (note that Figure 2 is displayed with a 10 point font instead of the 6.5 required for the listing output in Figure 1.) Additionally, there are many options for controlling ODS output available in Proc Report to further control single elements within the table with fonts, sizes, alignment or colors to highlight or emphasize components within the display.

Submission documents generated with Microsoft Word can then insert tables and listings in RTF format directly into original document before generating PDF output for submission.

DRAWBACKS TO ODS RTF

Naturally all this comes at a price... What's the catch? The main drawback to using RTF is that we get a single continuous table without page breaks. Since SAS has no way to determine how the table will be used in a document, there is no good way for SAS to assign page breaks within the table itself. This has a whole set of implications that programmers need to anticipate when creating tables that extend over more than one page. Issues to consider include:

Page-based summaries in Proc Report may not be correctly displayed

Proc Report tables will not repeat Group variable values at the start of a new page

Similarly, there are issues with titles and footnotes. Prior to SAS Version 8.2 titles and footnotes were placed in RTF headers and footers, and so would display on all pages of a table. This causes complications when a table is inserted into another document. In Version 8.2 the *bodytitle* option was added to the ODS RTF statement. This option makes titles and footnotes part of the document body, not in headers and footers. Consequently, titles and footnotes are not repeated after the first page of the display.

It also should be noted that certain features of proc report are disabled in all ODS output. (See SAS Note SN-002549.) Width assignments in Define statements are ignored when using RTF, and Proc Report makes up its own mind when assigning column widths. This is because width is specified in characters in the Define statement, and with RTF different fonts and sizes can be used, making width assignment a sticky issue for Proc Report to deal with. Break and Rbreak statements are also ignored. When the Skip option is used to break groups the blank lines are left out of the RTF file. These differences can be significant when working with existing Proc Report code that you want to convert

to use ODS. A carefully formatted table may look considerably different when run to an ODS destination.

USING ODS PDF

In SAS Version 8.2 the ODS PDF destination is in production. PDF is an especially useful output format since all eSub components are eventually rendered in PDF. Efficiencies can be gained in the publishing process by generating as much content as possible in PDF from the start. The ODS PDF destination uses SAS universal print driver to generate the PDF File and the printer style is the default style for this destination.

Programmers should take note of several issues with ODS PDF.

- The same Proc Report issues described for ODS RTF apply to ODS PDF
- ODS PDF does not embed fonts as specified in the FDA guidelines
- PDF files are not optimized

When the output pdf file is opened with Adobe Acrobat v4. and higher, an error message is displayed indicating that 'This file is damaged but is being repaired'. Per Technical Support SN-005481, this occurs because the SAS Universal Driver creates a PDFfile with an extra control linefeed character. Acrobat can read the file, and once opened the message will not re-appear the next time the file is opened. This should be corrected with the next version of SAS.

Bookmarks in the output PDF file can be generated automatically via SAS code using the ODS PROCLABEL option. However, a parent and child bookmark is created for each Proc Report statement. The contents of the child bookmark can be controlled with the contents= option in Proc Report.

ALTERNATIVE METHOD FOR PRODUCING PDF

Another option is to use an ODS Printer statement and define the printer as Acrobat Distiller. This method allows direct control of PDF content including optimization and font embedding using Distiller settings by using the Acrobat Distiller as the driver for generating the PDF. however, the ability to generate customized bookmarks using the SAS Proclabel statement is lost.

CONTROLLING OUTPUT APPEARANCE WITH ODS STYLES

For study report tables, the style attributes we are primarily interested in are font type and size, colors (background and font colors) and margins. We will discuss control of these elements at the ODS Style level using Proc Template. Several style elements that may be of interest, but are not discussed here, include cell spacing and padding, frames and borders. Also note that SAS procedures Report, Print and Tabulate allow direct assignment of ODS style elements within procedure syntax. This enables programmers to directly control style at the procedure level and to specify style attributes for specific regions of their reports with greater specificity than Proc Template allows (these procedures do not use templates).

Both ODS RTF and PDF use styles based on styles.printer by default. The default style for RTF output is the *RTF* style, while the default for the PDF destination is the *printer* style. Note that the style default is the parent of the style printer, which in turn is the parent of the style RTF. <see 'The Template FAQ – An Introduction to the RTF Destination' pg 18 of 18. > <also see 'The Template Procedure : Concepts' at www.sas.com/rnd/base/early-access/ODSdoc2/sashtml/tw5195/z1072349.htm page 1-2 of 23. Programmers can create their own styles to be used for both RTF and PDF output.

DEFINING A CUSTOM STYLE

Defining a custom style is discussed in the SAS Online Doc (3), in the Proc Template section of the Guide to the Output Delivery System.

A company can create their own style library and apply custom styles to their output using the following these steps.

1. create a custom style library
 - a. create a libname referencing the location of the new style library
 - b. add the library to the ODS path using the ODS PATH statement, be sure to specify Update mode
 - c. add styles to the library using Proc Template, defining styles using <libname>.<newstyle> syntax
2. reference custom styles in ODS statements by
 - a. including a libname for the custom library
 - b. referencing styles using <libname>.<newstyle> syntax

FONTS

Font name, font size and weight are associated with specific attribute names in the font list. Usually the first part of a style statement in proc template, the remainder of the style definition subsequently references the font definitions from the font list. This defines standard attributes to be used consistently for specific parts of ODS output. For example, *TitleFont* is used for display of all text generated by Title or Footnote statements. Font definitions are well documented in SAS Online Doc (3), under the Define Styles section of Proc Template. Also noteworthy is Page 151 of *Output Delivery System* by Lauren Haworth (2). This page summarizes the default major font elements and the output parts they control. This is a terrific page because one of the greater challenges of working with ODS is to find the style element you need to tweak to make your output do what you want. Some of the main Font Names used include

TitleFont – controls title and footnote generated text
 TitleFont2 – controls 'The xx Procedure' titles
 DocFont – controls display of table cells
 HeadingFont – control Table heading and footing fonts

For the example in Figure 2 we used the same font for all parts of the table, Times New Roman 10pt. To do this we use a replace fonts statement in our style, as below.

```
replace fonts /
  'TitleFont' = ("Times New Roman, Helvetica,
  Helv",10pt,Bold Italic)
  'EmphasisFont' = ("Times New Roman, Helvetica,
  Helv",10pt,Italic)
  'headingEmphasisFont' = ("Times New Roman,
  Helvetica, Helv",10pt,Bold Italic)
  'headingFont' = ("Times New Roman,
  Helvetica, Helv",10pt,Bold)
  'docFont' = ("Times New Roman, Helvetica,
  Helv",10pt)

  (Remaining styles.printer fonts... not used
  for our table but needed in statement)
```

Figure 3, a Proc Template Style fonts statement

When working with fonts programmers should bear in mind that

not all fonts exist on all machines, so consider font selection carefully when preparing reports that will be viewed in multiple locations. You can assign multiple font face definitions in an assignment statement (note use of Helvetica in example above). The first font on the list that is installed will be the one used.

COLORS

Proc Template style definitions control use of color in two parts. The 'color_list' statement defines the set of colors used and assigns them to variable names. The variable names are then used to define specific style elements in the 'colors' statement. This allows programmers to modify colors in a relatively simple manner by tweaking the color list only. Note that by convention, all color definitions in the default styles use 'fg' to note foreground colors and 'bg' to note background colors.

For our example table, we modified the header background color and changed the font color in the header. The colors are defined in the color_list statement shown below. In this case we reset the color used for header background (bgH) to a lighter shade of gray. The color is defined in RGB notation. We also added a new color for header text, named fgH, and set it to green.

```
replace color_list /
  'bgH' = cxE0E0E0
  'fgH' = green
  'link' = blue
  'fg' = black
  'bg' = white;
```

Figure 4, a Proc Template Style Color_list statement

Adding a separate foreground color, text color, for our purposes, that applies only to the header section required modification of the Colors statement to assign that color to the header foreground style element. This is shown below. Note that all color elements from styles.printer need to be repeated in this custom style definition.

```
replace colors /
  'headerfg' = color_list('fgH')

  (remaining colors from styles.printer)
```

Figure 5, a Proc Template Colors statement

Please note that the use of green font is not consistent with eSub standards and was done here for demonstration purposes only. The guideline (1) states on page 8, "We recommend use of a black font color. Blue font may be used for hypertext links (preferred for submissions to CBER). If a font color other than black is used, avoid light colors that do not print well on grayscale printers."

PAGE MARGINS

Page margins are assigned in a default element named Body. Styles.Printer leaves the margins undefined, so this is an important setting to be sure to specify. Margins can be specified in inches, as shown in Figure 7.

```
replace Body from Document
  "Controls the Body file." /
  bottommargin = 1.0in
  topmargin = 1.2in
  rightmargin = 1.0in
  leftmargin = 1.0in;
```

Figure 7, a Proc Template Body statement

IN-TEXT TABLES

Over the years companies have struggled with production of in-text tables. Populating these tables from SAS text-based output has been a challenge and many different approaches have been taken. ODS offers a good deal of help since we can now use SAS procedures to produce complete RTF tables ready for insertion into Word documents. Custom ODS styles can be developed and stored in a library, making it easy to apply standard styles that are consistent with internal report publishing standards.

REVIEWER-FRIENDLY REPORTS

Programmers should keep in mind that FDA reviewers often put documents onto their laptops for work off site. The displays on these machines may be more limited than the desktop displays we are used to working with. On a fifteen inch display, small text is even more difficult to read. Our goal should be to make the reviewer's life as easy as possible; a quicker review means a quicker approval!

One important consideration is that ODS output increases our ability to generate portrait-mode reporting instead of landscape. This has the potential to greatly enhance review-ability of study report tables but may require reworking of standard code and/or report standards at many companies. Those organizations currently developing standard report formats may want to consider establishing portrait-orientation ODS reports as a convention for SAS generated reports.

CONCLUSIONS

We hope this presentation has demonstrated how we can move from text-mode reports to ODS-based reports with relative ease. Proportional fonts, table grids and judicious use of color can help us to produce reports that are not only compliant with FDA guidelines, they are easier on the eye and more legible. We have shown how existing code can be modified to create ODS output to either PDF or RTF. ODS represents a big step forward in our ability to generate publication-quality reports with far less programming than has been required in previous SAS versions.

ODS can facilitate compliance with FDA guidelines but still has limitations. ODS PDF does not embed fonts as the guidelines specify, and Proc Report output in ODS has limitations in page based summarization and in formatting reports that cross pages. Our feeling is that this limitation is reasonable in an RTF file but since PDF is page-formatted there is no reason that Proc Report should not generate proper page summarizations and cross-page formatting. We urge the SAS user community to communicate with SAS Institute to strongly encourage them to improve these features in the next release of Base SAS Software.

Following this section we have listed many resources for ODS information, including user group presentations from past SUGI and PharmaSUG meetings.

REFERENCES

1. Providing Regulatory Submissions in Electronic Format--General Considerations, Food and Drug Administration, January 1999.
2. Haworth, Lauren E. (2001), *Output Delivery System: The Basics*, Cary, NC, SAS Institute Inc.
3. SAS Institute Inc.(1999), *SAS Online Doc, Version Eight*, Cary, NC, SAS Institute Inc.

ADDITIONAL ODS RESOURCES

PUBLICATIONS

- Bartleson, B.B. (2001), "Using SAS Version 8.1 Output Delivery System to Automate Two Sample Test Selection and Summarization," *Proceedings of the 2001 PharmaSUG Conference*.
- Bryant, L., Muller, S. and Pass, R. (2000) "ODS, YES! – Odious, No – An Introduction to the SAS Output Delivery System," *Proceedings of the Twenty-fifth Annual SAS Users Group International Conference*.
- Fehlner, W. (1998), "Making the Output Delivery System (ODS) Work for You", *Proceedings of the Twenty-fourth Annual SAS Users Group International Conference*.
- Gupta, Sunil K. (2001), "Using Styles and Templates to Customize SAS ODS Output," *Proceedings of the Twenty-sixth Annual SAS Users Group International Conference*.
- Haworth, L. (2001), "ODS for PRINT, REPORT and TABULATE," *Proceedings of the Twenty-sixth Annual SAS Users Group International Conference*.
- Heffner, W. F. (1998), "ODS: The Data Step Knows," in the *Proceedings for the Twenty-Third Annual SAS Users Group International Conference*
- Hull, Bob, (2001) "Now There Is an Easy Way to Get to Word, Just Use PROC TEMPLATE, PROC REPORT, and ODS RTF," *Proceedings of the Twenty-sixth Annual SAS Users Group International Conference*.
- Lafler, K.P. (1999) "Creating HTML Output with Output Delivery System," *Proceedings of the Twenty-fifth Annual SAS Users Group International Conference*.
- Lafler, K.P. (2000) "Output Delivery Tips, Tricks, and Techniques Using SAS Output Delivery System (ODS)," *Proceedings of the Twenty-fifth Annual SAS Users Group International Conference*.
- Laurencot, R.E (2000) "SAS® version 8 ODS for Drug Safety Reporting (Without Use of HTML)," *Proceedings of the 2000 PharmaSUG Conference*.
- McNeill, Sandy and David Kelley (2000), "Getting Stylish with Version 7 Base Reporting," *Proceedings of the Twenty-fifth Annual SAS Users Group International Conference*.
- McNeill, Sandy (2001), "Changes & Enhancements for ODS by Example (through Version 8.2)" *Proceedings of the Twenty-sixth Annual SAS Users Group International Conference*.
- McNeill, Sandy, Olinger, C.R. and Tobias, R. (2001) "The Basics of ODS and Templates for Data Analysis," *Proceedings of the 2001 PharmaSUG Conference*.
- Matange, Sanjay and Himesh Patel (2001), "New Visualization in V8.2," *Proceedings of the Twenty-sixth Annual SAS Users Group International Conference*.
- Olinger, C. (2000), "ODS for Dummies," *Proceedings of the Twenty-fifth Annual SAS Users Group International Conference*.
- Olinger, C. (1999), "Twisty Turny Passages All Alike-PROC TEMPLATE Exposed," *Proceedings of the Twenty-fourth Annual SAS Users Group International Conference*.
- Otsu, Hiroshi and Kitagawa, T. (2001), "Electronic Clinical Study Reports (e-CSR) using ODS in SAS® V8e," *Proceedings of the 2001 PharmaSUG Conference*.

Pass, R. (2001), "I'll Have the TABULATES a la ODS Please, With a Table of Contents On the Side," *Proceedings of the 2001 PharmaSUG Conference*.

Patel, H. and Matange, S. (2001), "New Visualization in V8.2," Olinger (1999)," ODS for Dummies ", *Proceedings of the 2001 PharmaSUG Conference*.

Slaughter, S.J. and Delwiche, L.D. (2001) "ODS for Reporting with Style," *Proceedings of the Twenty-sixth Annual SAS Users Group International Conference*

Synowiec, R.F (2001), "Data Visualization of Phase 1 Clinical Studies - "Big AI's World" or Using SAS ® Version 8 to Acquire Quality Ice Cream", *Proceedings of the 2001 PharmaSUG Conference*.

Ward, D.L. (2001) "Web-Enabling Your SAS Applications Using Only Base SAS®", *Proceedings of the 2001 PharmaSUG Conference*.

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ONLINE HELP ODS RESOURCES

Some information is available in Online Help.

- Sample programs are located in the Online Help Sample SAS Programs and Applications.
- Search for 'ODS', basic information on syntax of ODS statements is available

SAS ONLINE DOC RESOURCES

Extensive ODS information is available in Online Doc™. Note that this information does not reflect SAS 8.2 enhancements.

- 'Guide to the Output Delivery System' in the Base SAS Software folder. Of particular interest is the Proc Template chapter, which describes control of style elements.
- Proc Report documentation explains how to use style elements within Proc Report. Since Proc Report does not use a template programmers have direct control over ODS style elements within the procedure itself.

WEB RESOURCES AT SAS.COM

ODS Resources page in the BASE SAS Software Research and Development Web Site www.sas.com/rnd/base, contains a good deal of information including FAQs about ODS Printer and Proc Template.

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