



Science For A Better Life

Using Dynamic Lists in SAS Stored Processes for Genetic Toxicity Historical Control Data

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Agenda

- Example from Drug Development
 - Importance of Genetic Toxicity Testing
 - What are Historical Control Data?
- Enhanced Use of Metadata in SAS BI
 - Using SAS with SAS Stored Processes
 - Using Dynamic Lists in Metadata



Standardized Genetic Toxicity Testing

Genetic Toxicity Testing

- Part of safety assessment in Phase I of drug development
- Mostly done on animals
- Required by authorities after some very serious incidents (Contergan, 1961)

Standardized

- Based on a fixed protocol
- Evaluation based on sound statistical design and analysis
- Fixed conditions based on OECD guidelines
- Strictly audited by authorities

Structure of a Genetic Toxicity Test

The typical structure for a genetic toxicity test is

Group	Treatment	Dose level
1	Medium/solvent control	
2	Test substance	Low dose
3	Test substance	Mid dose
4	Test substance	High dose
5	Positive control	

- Responses of three doses of a test substance are compared to the responses of medium/solvent control to assess an effect of the substance.
- Responses of the positive control are compared to the responses of the medium/solvent control to assess the sensitivity of the assay.
- This setting may be repeated under different experimental conditions as
 - With or without metabolic activation
 - Pulse or continuous treatment



Control Groups

Control groups are

- Not treated with the substance to be tested
- Used to control the test system
 - to minimize the impact of possible extraneous variables
 - to recognize the possible presence of unwanted variables in the test system
 - assess the sensitivity of the test system

Responses seen in control groups should not vary from study to study, but could vary in different experimental setting (e.g. different labs).

Control types considered here:

- Medium: completely untreated
- Solvent: treated with the solvent of the substance
- Positive: treated with a dose of a substance with known effect



The Task

Historical Control Data

- Lists of control data of previous studies
- Statistics of the control data to be compared to the results of an actual study
- Reported for each study
- Yearly reports to see if experimental conditions are stable

SAS Stored Process Web Application

- Graphical User Interface to collect the data and report the statistics
- Accessible by an internet browser through the Intranet
- For each test and each lab of Bayer's genotoxicity testing groups

Initial Version of the Structure of a SAS Data Set for Historical Control Data



List

**Data base of historical control data for the In Vitro Micronucleus Test
sorted in descending order by study year and study number**

Study Year	Study Number	Metabolic Activation	Control Type	Experimental Part	Measurement Number	Cells Scored	Micronucleus containing cells [%]
2009	TOXT0079950	With	Medium	Pulse treatment	1	1000	0.8
2009	TOXT0079950	With	Medium	Pulse treatment	2	1000	1.1
2009	TOXT0079950	With	DMSO (1%)	Pulse treatment	1	1000	1.2
2009	TOXT0079950	With	DMSO (1%)	Pulse treatment	2	1000	1
2009	TOXT0079950	With	Cyclophosphamide (2 µg/mL)	Pulse treatment	1	1000	17
2009	TOXT0079950	With	Cyclophosphamide (2 µg/mL)	Pulse treatment	2	1000	19.2
2009	TOXT0079950	Without	Medium	Continuous treatment	1	1000	0.6
2009	TOXT0079950	Without	Medium	Continuous treatment	2	1000	1.6

Variables and formats

Variables in Table: HCDMNTINVITROBERLIN

Variable Number	Name	Type	Format	Label	Length
1	StudyNo	Character		Study Number	12
2	MetabolicActivation	Numeric	METABOLICACTIVATIONF	Metabolic Activation	8
3	ExperimentalPart	Numeric	EXPERIMENTALPARTF	Experimental Part	8
4	MeasurementNo	Numeric		Measurement Number	8
5	ControlType	Numeric	CONTROLSMNTINVITROF	Control Type	8
6	CellsScored	Numeric		Cells Scored	8
7	MeasurementValue	Numeric		Micronucleus containing cells [%]	8
8	StudyYear	Numeric		Study Year	8

Design Consideration for a SAS Stored Process “Add New Measurement”



As usual I used formats for the different experiment settings.

Their counterparts in the prompts were static list in the SAS Stored processes.

```
proc format;
  value ControlsMNTInVitrof
    1 = "Medium"
    10 = "DMSO (1%)"
    11 = "DMSO (2%)"
    12 = "Ethanol (1%)"
    13 = "Ethanol (2%)"
    14 = "0.9% NaCl (1%)"
    15 = "0.9% NaCl (2%)"
    16 = "0.9% NaCl (5%)"
    17 = "0.9% NaCl (10%)"
    18 = "Medium as solvent"
    20 = "Cylclophosphamide (2 µg/mL)"
    21 = "Cylclophosphamide (3 µg/mL)"
    22 = "Cylclophosphamide (Conc. still open)"
    23 = "Mitomycin C (0.05 µg/mL)"
    24 = "Mitomycin C (0.1 µg/mL)"
    25 = "Vinblastin sulfat (Conc. still open)";
run;

proc format;
  value MetabolicActivationf
    1 = "With"
    2 = "Without";
  value ExperimentalPartf
    1 = "Pulse treatment"
    2 = "Continuous treatment";
run;
```

Unformatted Value	Formatted (Displayed) Value	Default
1	Medium	☒
999	---Solvent controls---	☐
10	DMSO (1%)	☐
11	DMSO (2%)	☐
12	Ethanol (1%)	☐
13	Ethanol (2%)	☐
14	0.9% NaCl (1%)	☐

SAS Stored Process

Add new measurement – MNT in vitro



Firefox

SAS Logon Manager

Stored Processes

Home

Log Off Volker Harm

Stored Processes

sas

☐ Show only required items (denoted by *)

HCDGenTox - Add Measurement - MNT in vitro

Reset to Default

*Study number

*Study year

*Metabolic activation

With

*Experimental part

Pulse treatment

*Measurement number

1

*Control type

Medium

Medium

*Cells

—Solvent controls—

DMSO (1%)

DMSO (2%)

Ethanol (1%)

Ethanol (2%)

*% m

0.9% NaCl (1%)

0.9% NaCl (2%)

0.9% NaCl (5%)

0.9% NaCl (10%)

Medium as solvent

—Positive controls—

Cyclophosphamide (2 µg/mL)

Cyclophosphamide (3 µg/mL)

Cyclophosphamide (0)

Mitomycin C (0.05 µg/mL)

Mitomycin C (0.1 µg/mL)

Vinblastin sulfate (0)

Run

On execution of the SAS Stored process the following code is executed:

```
proc sql;
    insert into org.&DBName. (
        StudyNo,
        StudyYear,
        MetabolicActivation,
        ExperimentalPart,
        ControlType,
        MeasurementNo,
        CellsScored,
        MeasurementValue
    )
    values (
        "&StudyNo.",
        &StudyYear.,
        &MetabolicActivation.,
        &ExperimentalPart.,
        &ControlType.,
        &MeasurementNo.,
        &CellsScored.,
        &MeasurementValue.);
quit;
```

Design Consideration for a SAS Stored Process Maintaining the Database



Using the application over time the design showed several flaws:

- We defined some control types, for which the concentration was still not specified. So the list was longer than necessary.
- How to cope with new complexity by
 - Adding additional controls
 - Including new tests
 - Providing different labs with this application
 - Changing productive applications

So the requirement arose:

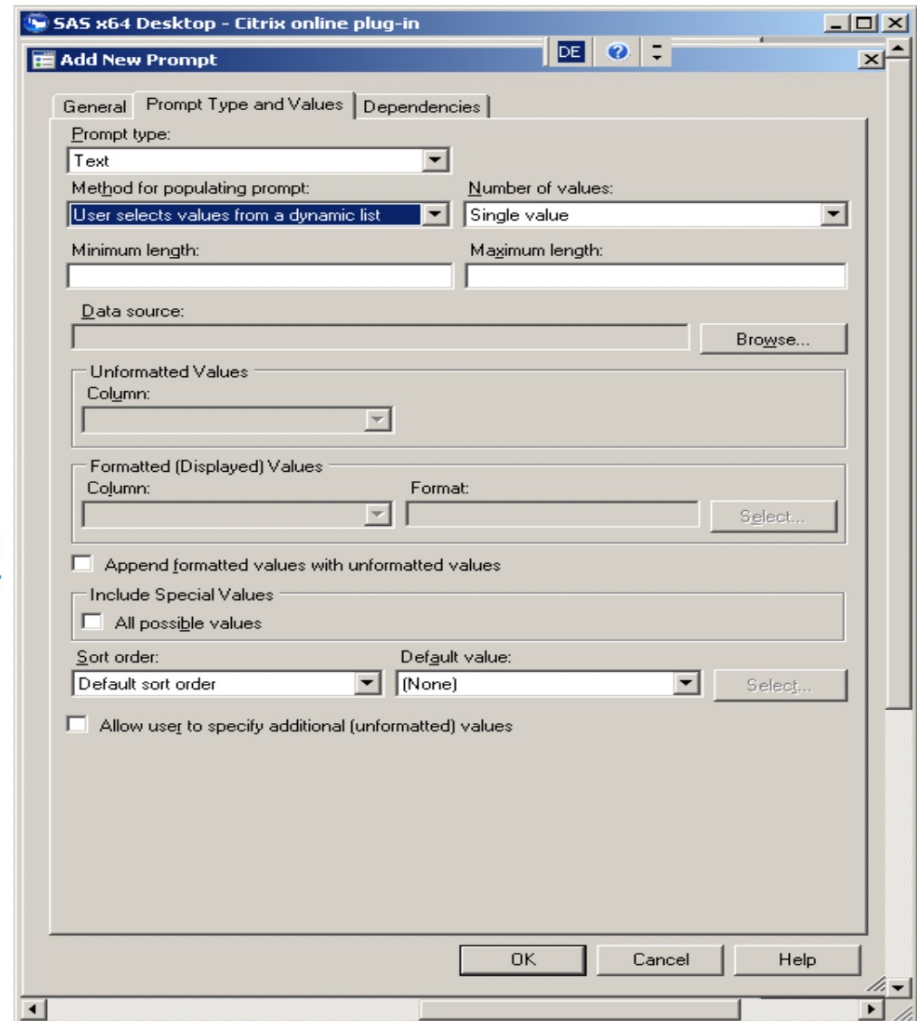
- Is there a way to make the design more dynamic by
 - Using only the established controls in the selection lists
 - Allowing the user himself to define new controls

Dynamic Lists

The SAS 9.2 prompt framework introduced two new prompt features that can help in this situation.

- Dynamic Prompts
 - Which allow the lookup of possible prompt values from a data set
- Cascading Prompts
 - Which allow possible prompt values to be dependent on the selected value of another prompt

These features are enabled by setting the Method for populating prompts to “User selects values from a dynamic list” in the prompt editor.





Prerequisites for using dynamic lists

Registering in metadata

- The data source used to look up the prompt values must be registered in the metadata of the SAS environment.
 - As the prompts of the stored process are executed before the SAS programs runs. Information about the data cannot be provided by the SAS program.

Adapt the data structure

- To use the dynamic lists conveniently I had to change the data structure of my databases.
 - Unformatted text values are a lot easier to handle in this context than formatted data.
 - To retain the structure implied by the formats a new variable was needed.

Registering a SAS Data Set as a Data Source



Two-step procedure done with the Data Library Manager in the SAS Management Console

- First step is to assign a library,
- Second step is to register the data set within the library.

How is it done?

- A “Getting started” how to do that can be found in the document “SAS Information Map Studio 4.2 Getting Started with SAS Information Maps”.
- More detailed instructions can be found in the document “SAS 9.2 Intelligence Platform Data Administration Guide”

Modifying the Structure of the SAS Data Set



Variables in Table: HCDMNTINVITROBERLIN

<i>Variable Number</i>	<i>Name</i>	<i>Type</i>	<i>Format</i>	<i>Label</i>	<i>Length</i>
1	StudyNo	Character		Study Number	20
2	StudyYear	Numeric		Study Year	8
3	MetabolicActivation	Numeric	METABOLICACTIVATIONF	Metabolic Activation	8
4	ExperimentalPart	Numeric	EXPERIMENTALPARTF	Experimental Part	8
5	ControlType	Numeric	CONTROLTYPEF	Control Type	8
6	XControlSubstance	Character		Control Substance	100
7	MeasurementNo	Numeric		Measurement Number	8
8	CellsScored	Numeric		Cells Scored	8
9	MeasurementValue	Numeric		Micronucleus containing cells [%]	8

Changes:

- The control substance is now of type text.
- The control type now contains information if the control is positive, solvent, or medium.

Reason for Changes:

- Select control substances dynamically from the existing substances in the table.
- Select dependent on the selected control type.

Modifying the Control Substance Prompt



General, Prompt Type and Values, Dependencies

SAS x64 Desktop - Citrix online plug-in
Edit Prompt

General | Prompt Type and Values | Dependencies

Name: ControlSubstance

Displayed text: Control Substance

Description: Select a control type from the existing ones depending on the control type

Parent group: WHCDGenTox - Add Measurement - MNT in vitro

Options:

- ☐ Hide from user
- ☒ Requires a non-blank value
- ☐ Read-only values
- ☐ Use prompt value throughout project

OK Cancel Help

SAS x64 Desktop - Citrix online plug-in
Edit Prompt

General | Prompt Type and Values | Dependencies

Prompt type: Text

Method for populating prompt: User selects values from a dynamic list

Number of values: Single value

Minimum length: Maximum length:

Data source: HCDMNTINVITROBERLIN

Unformatted Values

Column: <X>ControlSubstance

Formatted (Displayed) Values

Column: Use 'Unformatted Values' column

Format: Default format

☐ Append formatted values with unformatted values

☐ Include Special Values

☐ All possible values

Sort order: Default sort order

Default value: (None)

☒ Allow user to specify additional (unformatted) values

OK Cancel Help

SAS x64 Desktop - Citrix online plug-in
Edit Prompt

General | Prompt Type and Values | Dependencies

This prompt depends on the value of the following prompts:

Prompt	Description of Dependency
Control Type	HCDMNTINVITROBERLIN.ControlType = Value of "C..."

Dependency

Column: ControlType

Operator: =

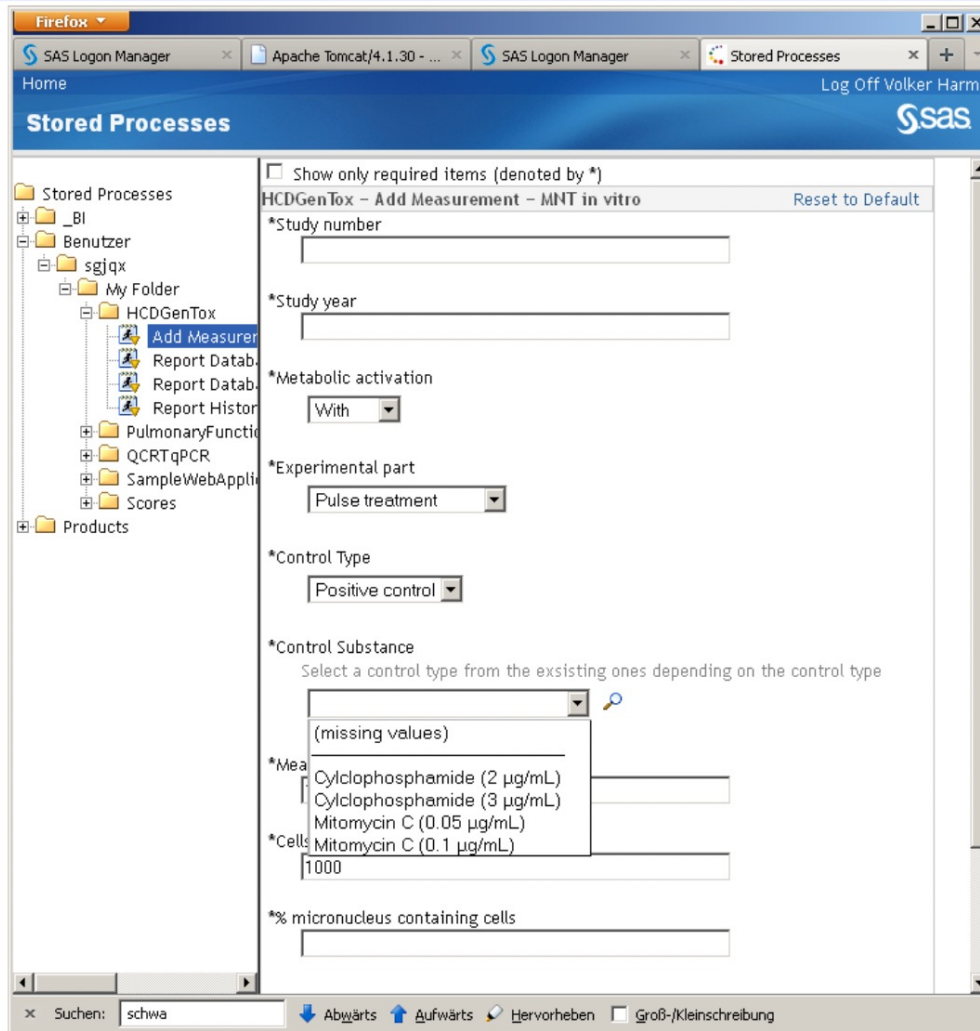
Value of: Control Type

The following prompts depend on the value of this prompt:

Prompt	Description of Dependency
No other prompts depend on this prompt	

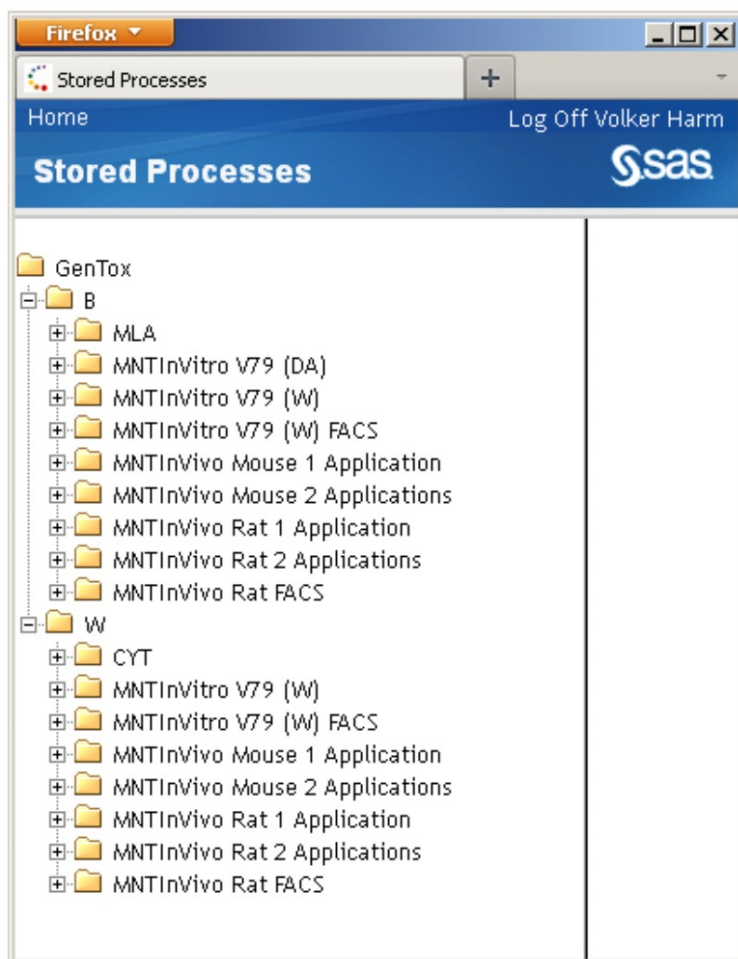
OK Cancel Help

The Modified SAS Stored Process



- Selection list for Control substance is built up from actual data in the database.
- Selection of possible values for the Control Substance is dependent on Control Type.
- New Control Substances can be added to the database and appear then in the selection.

Conclusion



Looking at the list of tests for which I have to implement the Historical Control Databases I feel much more comfortable with this new flexibility!



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Thank you!