

Ann Arbor Pharmaceutical Sciences
Pfizer Inc
170 Tabor Road
Morris Plains, NJ 07950



Global Research & Development

To: Richard Verseput, President
S-Matrix Corporation
Eureka, CA

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From: John Twist, Ph.D. MBA
Director of Business Operations

A handwritten signature in blue ink that reads "John Twist".

Subject: Validation of D.o.E. FUSION Software Package

Executive Summary

This document provides a high level description of our effort related to validating the D.o.E. FUSION software application. Pfizer's Software Development Methodology (SDM) was used to facilitate the validation process.

D.o.E. FUSION was selected after evaluating seven competing products. End user requirements were compiled and more than 180 test scripts were subsequently derived. Validation consisted of evaluating the software against these test scripts and carefully documenting all results. No problems were found in the verification that would prevent the release of S-Matrix D.o.E. FUSION for general use in designing and analyzing laboratory experiments. A small number of minor concerns were observed and communicated to S-Matrix. All of these concerns have been adequately addressed by S-Matrix.

New users are expected to complete the four tutorial examples included with the application before using the software in a production environment. Since the software accurately guides a non-statistician to create and analyze appropriate experimental designs, it is recommended that this software package be released for general distribution.

I. Business Needs

D.o.E. FUSION software was evaluated as a potential tool for designing experiments related to drug product development. Requirements included the ability to create efficient and recognizable designs for the types of experimentation typically encountered in an R&D environment (mixture, process, etc.). The software package also needed to be user-friendly to the extent that staff scientists (non-statisticians) could readily implement it with a reasonable amount of hands-on training. The intent was to provide a standardized and readily available software solution to the ever-present issues surrounding optimal resource allocation for synthesis, analytical and formulation/process development efforts.

II. Introduction to SDM Methodology (Software Validation)

System Development Methodology (SDM) is an internally developed set of guidelines for computer system acquisition/development. SDM is designed to improve resource management throughout this development process and provide consistent data and information management across the organization. The framework meets all FDA regulations and is additionally intended to provide clarity to responsibilities, requirements, and reporting commitments en-route to a successful development effort. Currently, version 3.0 is in use.

SDM recommends progression through 8 stages of the development process, each with its own set of deliverables.

1. **Initiation and Requirements Phase:** covers project initiation and the user's requirements gathering process.
2. **Design and Prototype Phase (Build):** facilitates modeling and prototype potential solutions. The prototype may eventually become the production system as any additional requirements are identified and built into the system.
3. **Pilot Phase (Purchase):** occurs if available software and/or hardware products can meet client needs without further modification of the source code. This is determined by how well the requirements are met by a particular commercial product. Typically, several competing products are compared based on features and ease of use and the top candidate is evaluated.
4. **Integration:** occurs if no single existing computerized system can adequately meet the requirements. Integration is the process of combining existing or purchased software and/or hardware products to meet the users' requirements. It should involve minimal programming compared to a customized system built from internally developed source code.
5. **User Acceptance Phase (Validation):** involves user testing and training for the purpose of gaining acceptance of the new system by the client. All functions/routines which will be accessed by the end-user of the product must be evaluated. Additionally, this phase of the project involves documentation updates for users and system support staff.
6. **Implementation Phase:** is the formal turnover of the system to colleagues and operations. This involves production system installation, system verification, and the creation of final documentation.
7. **Maintenance Phase (Change Management):** occurs when a change (i.e. an enhancement or bug fix) is requested for a production application. As part of this process, existing SDM deliverables are updated to reflect the changes.
8. **Retirement Phase:** occurs when the system no longer meets the need for which it was developed and is removed from use in production.

The pilot phase involved evaluation of seven competing products (D.o.E. Fusion, Design Expert, StatGraphics, E-Chip, JMP SAS, Minitab, and Trial Run). The selection criteria included: scope of available designs, ability of software to guide the user to an appropriate design, data analysis capabilities and connectivity to MS Office applications (Excel, Word and PowerPoint). D.o.E. FUSION software topped the rankings and was subsequently purchased and evaluated via SDM. The software was validated in-house for user-acceptance through the execution of test scripts designed to encompass all user requirements.

III. Test Script Summary

Verification Test Scripts Summary Table

| Verification Category | Number of Test Scripts | Passed | Failed | Not Tested |
|-----------------------------------|------------------------|------------|-----------|------------|
| Vendor Responsibilities | 4 | 4 | 0 | 0 |
| General | 35 | 32 | 2 | 1 |
| Experiment Design | 82 | 69 | 4 | 9 |
| Data Analysis & Response Graphics | 47 | 38 | 0 | 9 |
| Multiple Response Optimization | 13 | 10 | 1 | 2 |
| Total | 181 | 153 | 7* | 21+ |

* - See Section IV Part A below.

+ - Not Tested scripts relate to additional features being developed under a Pfizer grant (see Section VII).

IV. Major Observations/Findings

A. No problems were found in the verification that would prevent the release of S-Matrix D.o.E. FUSION for general use in designing and analyzing laboratory experiments. Minor problems meeting our requirements were found with the following test scripts. These problems are described below along with the vendor's corrective actions.

1. There was no pre-launch test program to identify DLL's that are out-of-date. This is an installation utility and does not effect the operation of the program.

Vendor Corrective Action: A "Version Checker" pre-launch program was created for all versions of D.o.E. FUSION that checks the Windows registry and then confirms the presence of the required DLLs and OCXs prior to launching D.o.E. FUSION. The program provides a warning when one or more of the required files can not be found. The Version Checker pre-launch program is available in D.o.E. FUSION, versions 6.7.0 and later.

2. Although reports can be exported to MS Word, too much formatting is required. Vendor is developing a better procedure to import D.o.E. FUSION PRO reports into MS Word.

Vendor Corrective Action: A print-to HTML file option was implemented that preserved the report content layout and table formatting. The HTML file can be opened directly in Word or PowerPoint, and is compatible with the Office 95, 97, and 2000 products. This feature upgrade is available in D.o.E. FUSION, versions 6.6.1 and later.

3. A run-time error occurred when generating a Model-Robust Mixture-Process procedure with Optimization when there are 3 mixture variables, and 3 process variables in which one of the process variables was a categorical variable. This was a bug within the model robust design generator that will be fixed in the next maintenance release.

Vendor Corrective Action: This special-case problem in the model-robust design generator has been fixed. The correction is available in D.o.E. FUSION, versions 6.7.0 and later.

4. One of our requirements was that replicate data points be identified in the graphs. D.o.E. FUSION PRO software does not identify replicate points in its graphs. They are identified in the "Design Properties Settings" report. The vendor plans to include this feature in the first upgrade scheduled for Q1 2001.

Vendor Corrective Action: Pfizer set a low priority on the development of this feature. This change therefore has been scheduled for a future upgrade.

5. Blocking in the Model-Robust Process procedure. Although this test script meets the Expected Results, it was failed because of the uneven distribution of runs between the blocks using the default value for the "No. of degrees-of-freedom points". Block 3 had 26 runs in it, one less than a design without blocking. This defeats the purpose of blocking. However, a more even distribution of runs between the blocks can be obtained by using 6 or 7 runs for "No. of degrees-of-freedom points". S-Matrix will investigate possible modification in the blocking strategy that will allow for a more even distribution of runs between the blocks.

Vendor Corrective Action: This issue is a result of the requirement that the Model-robust Optimization designs always contain the Model-robust Screening design points as part of the optimization design. After discussions with Dr. Douglas Montgomery and Dr. John Cornell, it was agreed that this requirement overburdened the design when the design is internally blocked. This change will be implemented in the next release of the product (version 6.8.0 or later).

6. Creating a "Lab Ready" worksheet. Although a data entry spreadsheet can be printed out as a worksheet, there is no way to enter a header or other information in order to be a "Lab-Ready" worksheet. A worksheet could be created by copying the data entry spreadsheet and pasting it into an Excel or MS Word.

Vendor Corrective Action: The Project Header data available in all other D.o.E. FUSION report printouts will be added to the Response Data Collection report printout. Pfizer set a low priority on the development of this feature. This change has therefore been scheduled for a future upgrade.

7. Optimization Search with multiple responses and multiple constraints. This test required the optimization results to be within the optimum region presented in Figure 14-14 on page 599 of Design and Analysis of Experiments (1997) by Montgomery. The Boundary conditions are $Yield \geq 78.5$, $62 \leq Viscosity \leq 68$, and $Molecular Weight \leq 3400$. D.o.E. FUSION boundary conditions were set to: $78.5 \leq Yield \leq 100$, $62 \leq Viscosity \leq 68$, $2500 \leq Molecular Weight \leq 3400$. For a starting point where $Temp=170$, the optimum point converged to the lower region in Figure 14-14. However, for $Temp=175$ or 180 , the optimum values converged to values outside of the boundary conditions. The optimization procedure was operating correctly. The problem was selecting too large a value for the upper limit of Yield causing problems with the desirability function. The vendor will add a Warning Message when the default limits are increased. In addition, optimization graphics are currently being developed for D.o.E. FUSION and are expected to be in the first upgrade scheduled for Q1, 2001.

Vendor Corrective Action: The program provides a warning when the user defines response optimization goals that are significantly outside the observed response data ranges. The Version warning message feature is available in D.o.E. FUSION, versions 6.7.0 and later.

Development of a Graphical Optimizer feature with color and B&W optimization overlay graphics was completed in March 2001. This feature will be available in the next release of D.o.E. FUSION (version 6.8.0 or later).

B. Comments for the testing of this version of the software

1. The tutorials were found to be an excellent tool for learning the operation of this software. It would be useful to have a tutorial for mixture or mixture-process design. A mixture and/or mixture-process tutorial is scheduled for a Maintenance Release of FUSION PRO.

Vendor Response: A combined Mixture-Process design tutorial has been developed for FUSION PRO, the professional edition of D.o.E. FUSION offering mixture and combined mixture-process D.o.E. capabilities. The tutorial utilizes the data from Example 7.1 in Cornell, John A., Experiments With Mixtures, Second Edition, John Wiley and Sons, New York, 1990. The tutorial is available in D.o.E. FUSION, versions 6.7.0 and later.

2. Most of the problem printing past a cell border in the reports has been corrected by using a smaller font size. However, there were some instances when the last line did not print the bottom half of the text. This only occurs with a postscript driver and does not appear to be a problem printing with PCL drivers.

Vendor Response: Problems with printing past cell borders have been fixed. The correction is available in D.o.E. FUSION, versions 6.6.1 and later.

3. The program has excellent graphs that can easily be imported into MS Word. The Enhanced Metafile format is recommended; however, the bitmap format is also acceptable.
4. The "Matrix Master Wizard" uses the maximum and minimum values to create the coded variables (max → +1 and min → -1). For a rotatable central composite model, the maximum and minimum values are the axial or star points. Normally the factorial points are assigned the +1 and -1 coded variable. It would be beneficial if the "Matrix Master Wizard" would allow the user to change the values for the maximum and minimum values and create the coded variables accordingly. This would be important if a value had to be changed requiring the "Matrix Master Wizard" to be run for a CCD design.

Vendor Response: An extensive evaluation of this issue has shown that D.o.E. FUSION provides a correct data analysis and identical response surface graphs and optimization results regardless of whether the data are analyzed as a classical CCD design or as a reconciled historical or edited data matrix via the Matrix Master Wizard. Pfizer therefore set a low priority on any need to modify Matrix Master functionality in the special case of edited CCD designs.

V. Recommendations for Use

D.o.E. FUSION has been found to do a laudable job of creating and analyzing a variety of *experimental* designs. Excellent graphical capabilities, user-friendliness, and the ability to handle combined mixtures and process designs make this product our best available software solution. Since no major defects were found to exist, it is recommended that this software package be released for general distribution.

An electronic copy of the User's Manual is automatically installed on each PC during software installation. The manual can be printed or used online. Additional online help is also available. The User's manual includes a detailed tutorial with three sample designs. New users are expected to complete the three tutorial examples before using the software in a production environment. Further assistance and training in the area of experimental design will be provided as needed by the Strategic Operations Management group.

VI. Future Actions

All findings during the validation effort have been documented and communicated to the vendor (S-Matrix). No critical findings were observed during the validation effort. The majority of the issues, all non-critical, have been addressed by a maintenance release 6.6.1. Remaining issues will be addressed in a future release of the software (i.e. version 7.0).

VII. Future Direction of the Software Supported by a Pfizer Grant

Item 1: Normal Probability Plots of Experiment Variable Effects

Completed in Q4, 2000

The current CARD 5.1 software program provides mean effects estimation results in the form of tabulated statistics with appropriate hypothesis tests and confidence intervals. Interpretation of these statistics is facilitated by S-Matrix's PlainTalk Report technology and Variable Effects ranking tables and charts. However, many DOE texts and some software also provide normal probability plotting to aid in identifying and visualizing important effector variables.

This capability enables the experimenter to easily generate normal probability plots of variable effects. The qualitative specification for this capability is based on the following publication:

1. Montgomery, Douglas C., (1996), Design and Analysis of Experiments, 4th Edition, John Wiley and Sons, New York (specifically pages 318-336).

Item 2: Split-Plot Experiment Design and Analysis

Delivered for Beta Testing in Q1, 2001

Current DOE software does not correctly estimate the experimental error in multifactor, blocked experiments in which there is a restriction on randomization within the blocks. This in turn can lead to incorrect hypothesis testing of variable effects.

This capability enables the experimenter to generate experiment designs that correctly address additional restrictions on within-block randomization. The capability extends to correct experimental error and variable effects estimation.

The qualitative specification for this capability is based on the following publications:

1. Montgomery, Douglas C., (1996), Design and Analysis of Experiments, 4th Edition, John Wiley and Sons, New York (specifically pages 521-529).
2. Cornell, John A., (1990), Experiments With Mixtures, 2nd Edition, John Wiley and Sons, New York (specifically pages 365-377).

Item 3: Dispersion Effects Estimation In Factorial Designs

Scheduled for Q2, 2001

Most DOE analyses focus on isolating and quantifying experiment variable mean effects. Software programs use regression or ANOVA analysis, coupled with the appropriate hypothesis tests, to identify important variables in terms of their mean effect on the response. However, these analyses do not estimate the effects of the variable on product stability or quality variation. These effects are called dispersion effects. A variable identified as not having a significant mean effect from the standard analyses may still be an important effector in terms of dispersion effects. Without this information, the experimenter may prematurely dismiss a variable that has important effects on product stability or quality.

This capability enables the experimenter to estimate the effects of experiment variables on product stability and quality variation in replicated and unreplicated two-level factorial designs. The qualitative specification for this capability is based on the following publications:

1. Box, George B. P., and Meyer, Daniel R. (1986), "Dispersion Effects From Fractional Designs," *Technometrics*, 28, 19-27.
2. Nair, Vijayan N. and Pregibon, Daryl. (1988), "Analyzing Dispersion Effects From Factorial Experiments," *Technometrics*, 30, 247-257.

Item 4: Sequential Optimization by Method of Steepest Ascent

Scheduled for Q2, 2001

Current DOE software treats each experiment in isolation. The user is required to extrapolate the results of a given study to the construction of a "next" experiment. Although the relevant data and tabulated results required for such an extrapolation are already contained in the software, the extrapolation often requires a DOE subject matter knowledge beyond that of the general user.

This capability enables the experimenter to obtain a suggested next experiment based on (1) the estimates of variable effects, (2) the multiple optimization results, and (3) the desirability ranking and relative importance weighting of the analyzed responses.

The qualitative specification for this capability is based on the following publication:

1. Montgomery, Douglas C., (1996), *Design and Analysis of Experiments*, 4th Edition, John Wiley and Sons, New York (specifically pages 578-584).

Item 5: Stability Study Experiment Design and Analysis

Scheduled for Q3, 2001

Currently no expert-system DOE software programs exist that provide correct stability design and analysis. The result is that many stability studies are either "overpowered" or "underpowered" with regard to the amount of work performed and the completeness and defensibility of reported results. Ultimately this translates into a greater cost than is required (overpowered study) or delays with associated costs while the deficiencies in reported results are made up.

This capability enables the experimenter to select a stability experiment design that is in agreement with FDA requirements and is cost optimal given the required scope of the study. The qualitative specification for this capability is based on the following publications:

1. Nordbrock, Earl. (1992), "Statistical Comparison of Stability Study Designs," *Journal of Biopharmaceutical Statistics*, 2(1), 91-113.
2. "Stability Testing of Drug Substances and Drug Products," Draft Guidance for Industry, (June, 1998). USDHHS, FDA, CBER, CDER.