



GAMP4 and Process Simulation Software

Process Simulation Software for operator training and system testing is a valuable tool for process automation projects. Users in validated industries are interested in how the use of Process Simulation Software is impacted by their adoption of the GAMP4 Guide for Validation of Automated Systems. When used correctly, Process Simulation Software can help companies with validated systems comply with GAMP4 guidelines by:

- Providing more comprehensive testing of the process control system, resulting in better automation system performance.
- Accelerating the System Acceptance Testing phase of a project, resulting in shorter project cycles and quicker time to market.
- Mitigating risk by more comprehensive system testing.



This paper discusses the following:

- GAMP4 guidelines concerning the use of Process Simulation Software.
- Impact of system testing and qualification using Process Simulation Software.
- Impact on project risk mitigation using Process Simulation Software.
- GAMP4 requirements for suppliers of Process Simulation Software.

GAMP4 Guidelines for the Process Simulation Software

The GAMP4 guidelines clearly state that the use of process simulation is acceptable for system testing. The guidelines state that factory testing may be "...carried out without connection to field instrumentation and may include an agreed level of process simulation".ⁱ GAMP4 also gives guidelines for the suppliers of Process Simulation Software, which will be covered later in this paper. Process simulation is therefore an acceptable tool for testing validated systems and for ensuring completeness of testing.

Several requirements for system testing lead to the use of process simulation for validated systems testing.

- The first requirement is that the "...software is frozen prior to testing."ⁱⁱ It is important that final software modifications are completed prior to testing and that the tested software is not modified or changed after testing. This applies in particular to the Software Integration Testing and System Acceptance Testing phases of the project.
- The second requirement is that application software, which is no longer needed, should be removed prior to system testing, in order to avoid "dead" code. The guidelines are clear: "dead" code is defined as application software that is "...left over...from development or code changes."ⁱⁱⁱ The only instance in which unused code can be kept in the application software is when it is

used for future “...purposes of testing or for later diagnosis during support work...”^{iv}, in which case it should be labeled, commented out, and documented. Application software used specifically for simulation has no purpose once testing is complete and must be removed prior to Software Integration Testing and System Acceptance Testing.

These two requirements dictate the use of a non-intrusive testing interface, especially for Software Integration Testing and System Acceptance Testing. A non-intrusive testing interface:

- Allows the application software to run in a normal mode without any modification during testing. This same tested application software can then run in a normal mode in the process controller without modification.
- Provides an external interface to the application software that does not require any additional code for testing. When testing is completed, the non-intrusive interface can be shut down and no removal of “dead” code is required.

Process Simulation Software utilizing non-intrusive interfaces meets the requirements of the GAMP4 guidelines for process control system testing.

Impact of System Testing and Qualification Using Process Simulation Software

Testing is a critical aspect of implementing a process control system in compliance with GAMP4 guidelines. The cost of testing and validating a process control system can equal or

exceed the application software development. In addition, testing has a major impact on project schedule and time to market. Process Control System testing is broken down into several categories by the GAMP4 guidelines. The use of Process Simulation Software can assist the validated user and supplier during the Software Integration Testing and System Acceptance Testing phases of Installation Qualification (IQ) and Operational Qualification (OQ). The correct use of Process Simulation Software can have a positive impact on system testing by providing an environment for:

- More complete and accurate testing of the process control system. Medium-fidelity process models (mass balance, heat balance) have been used to provide realistic testing of validated control systems, resulting in installed automation systems that make better quality product with higher yields as soon as possible after System Acceptance Testing. The result is the user of a validated system meets production and project goals quicker.
- Compression of project schedule and reduced time to market through reduction of on-site System Acceptance Testing. During the Software Integration Testing phase, the GAMP4 guidelines allow testing, using Process Simulation Software, to be included as “...part of subsequent IQ/OQ evidence if adequately controlled and documented. This can help reduce the amount of testing needed on-site at a later time, particularly in software OQ.”^v By moving parts of the System Acceptance Testing to an off-line system using Process Simulation Software, the project schedule can be

effectively compressed, resulting in an earlier time to market.

The use of Process Simulation Software can have a great impact on the success of a validated process addition or process expansion project.

Impact on Project Risk Mitigation using Process Simulation Software

One of the benefits of following the GAMP4 guidelines is a structured way of assessing and mitigating risk for the validated system. In addition to the business benefits of following the GAMP4 guidelines, a second benefit is to "...avoid any intolerable risk to patient safety or to the business."^{vi} The use of Process Simulation Software is an effective tool for addressing identified areas of risk by providing a realistic environment for:

- Training operations staff on critical or risky process operations without effecting process integrity.
- Testing failure modes of batch processes or critical batch phases without effecting process integrity.

The investment in Process Simulation Software for process control system testing and operator training can usually be justified by the benefits of mitigating risk alone due to the high value of product and cost of downtime in the validated industries. Typical justifications may be:

- Reduction of off-spec batch: typically, \$1,000,000 savings per saved batch.
- Reduction of unscheduled downtime: typical savings of \$50,000 per hour downtime.
- Reduction of FDA violations, OSHA violations, and EPA violations: typical fines of \$100,000 and up.

GAMP4 Requirements for Suppliers of Process Simulation Software

The GAMP4 guidelines distinguish between the process control system validation requirements and the validation requirements of tools such as Process Simulation Software. "Tools supporting the system development and management process, rather than the business processes themselves, are not GxP applications, and do not require formal validation..."^{vii} However, the guidelines state that the tools and the supplier of the tools should be well chosen.

In general, the requirements of Process Simulation Software for the validated industries are:

- The supplier should have a documented software development and quality program that complies with industry best practices quality systems.
- The Process Simulation Software should be applicable for process control system testing and operator training and not designed primarily for other uses (such as process design).
- The Process Simulation Software should be a "...commercially available, standard tool..." that is not "...highly-customized for use..."^{viii} The application should be delivered as object code or executable programs and not require the user to modify source code under standard use. If the tool requires the user to modify source code, or the simulation package requires 3GL programming, the tool falls into the same validation requirements as "bespoke" tools and "...greatly increased scrutiny and documented verification of its fitness for purpose is required."^{ix}



ⁱ Section 9.13, GAMP 4 Guide for Validation of Automated Systems, December 2001, Copyright ISPE 2001

ⁱⁱ Section 9.10, Ibid

ⁱⁱⁱ Appendix D5, Section 3.1.8, Ibid

^{iv} Appendix D5, Section 3.1.8, Ibid

^v Section 6.2, Ibid

^{vi} Appendix M3, Section 1, Ibid

^{vii} Appendix M4, Ibid

^{viii} Appendix M4, Ibid

^{ix} Appendix M4, Ibid

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