GAMP 5 and Dynamic Process Simulation

By following the guidance document Good Automated Manufacturing Practice (GAMP) 5, pharmaceutical manufacturing facilities can use a comprehensive approach to maintain their computerized systems while reducing risk to patient safety. GAMP 5 also provides a risk-based approach to testing by breaking up computerized systems into different categories, which range from non-configured out of the box product to a custom application, that require certain detailed levels of testing (Category 3, Category 4, Category 5). Many pharmaceutical manufacturing facilities utilize dynamic simulation for automation code projects or improvements, as well as training on different automation platforms, Manufacturing Execution System (MES), and operator training on the process itself. This paper will discuss how dynamic simulation can be used to train users more effectively, achieve more comprehensive testing of code, reduce automation risk , and enhance operation's process understanding, while following these GAMP 5 guidelines.

Dynamic Simulation Solution

What is Dynamic Simulation?

Dynamic simulation provides a real-time, first principles-based model of processes that take place within a plant. Kinetics, thermodynamics, hydraulics, mass and heat balances are used in the model to simulate how the process responds to different flows, temperatures and other variables that could be experienced in a live production setting. By using P&IDs, equipment specifications, process equipment data or operating conditions, a dynamic simulation model can be tuned to reflect how the process would act on the plant floor. The more data that is added to the model, the higher the fidelity and closer it will respond to the live process; however, the maximum value of applying a dynamic simulation model isn't always achieved with the highest level of fidelity.

Importance of Process Modeling

Traditionally, many existing production sites use tieback models, or simple loop models, in order to simulate their controls in an offline environment. These tieback models are an oversimplification and, as a result, do not represent how controls would respond when commissioned on the live production system. They can only simulate static values for uncontrolled IO (e.g. temperature input reading of 50 degrees Celsius) and directionally correct process response for loop IO (e.g. valve closed status input when valve setpoint has been set to close or the flow changing in response to a PID output). These capabilities for a tieback model allow for fundamental testing of the control system configuration.

A dynamic process model constantly calculates the material and energy balances and the pressure-flow network of the simulated offline process in order to be responsive to variable changes. This first-principles based process is primarily modeled off equipment and plant design specifications to allow for a similar representation of the process. Dynamic process models combine and approximate rigorous equations into a small set of simplified equations that are customized for each process and facility. Although most dynamic process models don't utilize complex relations used in more complex models such as reaction kinetics or vapor-liquid, the use of empirical relationships helps medium fidelity models achieve higher capabilities than a traditional tieback model provides. To ensure the dynamic model behaves reliably, the GAMP 5 software development model can be applied ensuring design inputs to the model, configuration and testing deliver a successful simulation. By pairing this dynamic simulation model with a copy of the exact control logic of the production system, both the process and controls can be simulated, creating a true offline version of a facility.

Benefits of using Dynamic Simulation:

Operator Training

Traditionally, operators are trained through classroom setting courseware and secondhand experience by shadowing experienced operators during their shifts. Although there are lessons to be learned from this approach, it requires a high amount of time and attention from current operators to teach new operators about the process. Using a dynamic simulation, operators can learn how to start batches and correct responses to process upsets. This provides them with a more comprehensive way to learn about the process first hand in a conducive environment, rather than a second hand classroom setting approach. Operations staff are trained on critical or risky process operations, reducing the risk of operations not responding properly to process upsets.

GAMP 5 guidelines highlight the importance of training on operational process and procedures prior to live operation. "As part of preparing for final acceptance and formal handover for live operation, the regulated company should ensure that appropriate operational processes, procedures, and plans have been implemented, and are supported by appropriate training"[1]. An offline training environment which utilizes dynamic simulation is an effective tool in training operators on processes before "formal handover for live operation" as well as accelerating operator competency. A dynamic simulation training system can simulate abnormal situations and allow the operator to experience process events, run batches, and other abnormal situations they may not regularly experience on the production floor.

"The regulated company should therefore…evaluate the effectiveness of the training…maintain appropriate training records"[2]. The effectiveness which a dynamic simulation model can bring to training can be measured by metrics such a material saved by training in this offline environment, acceleration of operational competency, reduction of batch holds, and additional batches/campaigns completed. Training can be recorded by what situations operators were trained on, and how well the operators responded and effectively diverted the problem. These records can be maintained independent from the dynamic simulation model or built into the model to automatically generate reports.

The investment in a dynamic simulation model for operator training can be justified alone by the benefits of mitigating risk due to the high value of product and cost of downtime:

- Reducing off-spec batches – typically, $1,000,000 savings per saved batch
- Reducing unscheduled downtime – typical savings of $50,000 per hour downtime

System Testing and Qualification

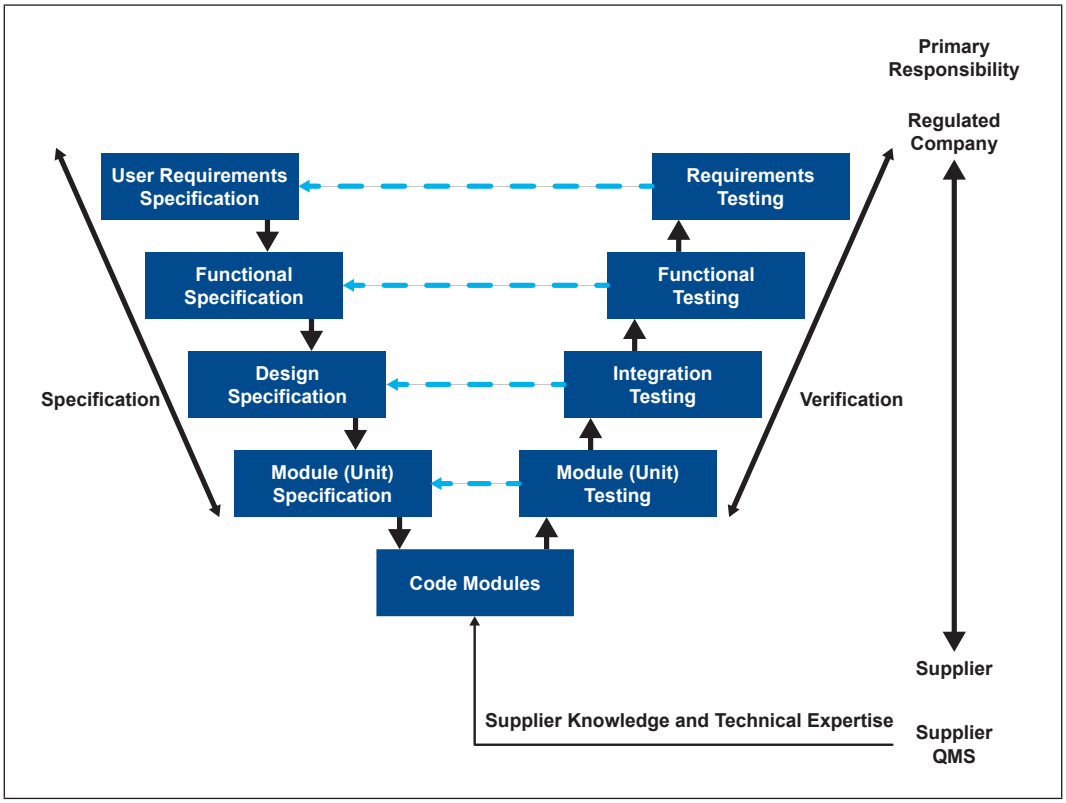

Figure 4.4: Approach for a Custom Application (Category 5), GAMP 5 A Risk-Based Approach to Compliant GxP Computerized Systems, Copyright ISPE 2008

Testing is a critical aspect of implementing a process control system in compliance with GAMP guidelines. “Testing also may take place to meet other business or legal requirements, such as safety, health, environment, and finance such as SOX. If so, unnecessary duplication of testing should be avoided”[3].

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 GAMP guidelines. The use of process simulation software can assist the user and supplier during the Software Acceptance Testing and Site Qualification Tests.

At many facilities that rely on the GAMP 5 guidelines, their validation procedures allow for FAT testing to be leveraged during the site qualification phase. “Wherever possible, regulated companies should clearly communicate to suppliers the testing and document requirements in advance such that supplier test documentation is of the required standard to support compliance activities”[4]. The reuse of test results is dependent on-site validation requirements, as well as suppliers following testing protocols and documenting results in a way that the regulated company can leverage.

If pharmaceutical manufacturing facilities use dynamic simulation to comprehensively test automation code during Design Build Test (DBT), FAT and SAT, they will have more efficient and effective engineering runs and water batches, reducing the total timeline to their first salable lot. Traditionally, simple tiebacks are used for DBT, FAT, and SAT and provide an evaluation that only reviews control strategies independent of one another while forcing IO. Applying a dynamic simulation model during these tests allows each control strategy to be reviewed as if they were running on a live facility, which also provides a simulated environment to test batch recipes, interlocks, and other functions that require multiple steps more comprehensively.

When applied correctly and early in the project, dynamic process simulation can help companies achieves these possible testing and quality benefits:

- Improved automation system performance due to more comprehensive testing of the process control system
- Shorter project cycles and quicker time to market due to an accelerated System Acceptance Testing
- Mitigated risk during qualification and commissioning by more comprehensive system testing
- Reduced time to production from a few days to as many as six weeks

Quality Risk Mitigation

The benefit of following the GAMP guidelines is a structured way of assessing and mitigating quality risk for the validated system: i.e. "…identification and management of risks to patient safety, product quality, and data integrity"[5].

During the Quality Risk Management process, "It may be necessary to perform a more detailed assessment that analyzes further the severity of harm, likelihood of occurrence, and probability of detection"[6]. The use of dynamic simulation is an effective tool for mitigating identified areas of risk by providing a realistic environment for testing at an early stage in software development. Failure modes of batch processes or critical batch phases can be tested without effecting process integrity. Dynamic 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.

During the Factory and Site Acceptance Tests, "There may be a need for specific tests to satisfy contractual requirements… these are a pre-defined set of functional tests that demonstrate fitness for intended use and compliance with user requirements. In such circumstances the test strategy should leverage these tests to satisfy GxP verification requirements and avoid duplication."[7]. The ability to leverage testing at multiple points allows the user to complete Factory and Site Acceptance Testing in a shorter amount of time.

"When using test environments, the test strategy chosen should justify the equivalency of test results, i.e., justify that similar results would have been achieved in the operational environment" (Page 203). A dynamic simulation model can provide an equivalent testing environment because it is built by using P&IDs and relevant process data. Using the risk-based approach, more value from the FAT can be capitalized due to the more realistic testing environment. Hence, the project schedule can be effectively compressed, resulting in an earlier time to market. The use of process simulation software can have a significant impact on the success of a validated process addition or process expansion project.

Lifecycle benefits

Beyond new projects, dynamic simulation can provide users with a tool to help with efficient change management throughout the life of the facility. Today, most processes are highly automated and require less human interaction and decision making. In order to make sure that changes to the automation system do not impact the overall process, it is best to review proposed changes in an offline, dynamic simulation model. Changes may come as a result of an incident on a plant instance. GAMP 5 expects "incidents should be assessed for any impact on patient safety, product quality and data integrity" (page 242). The dynamic model can be used to replay the incident, evaluate operator responses at the time, and generate improvements based on this analysis. Operators can also continue to use the dynamic simulation to train on the process and learn new Standard Operating Procedures (SOPs).

When dynamic simulation is used on-site for the life cycle of a facility, the following values can be achieved:

- Testing code changes, batch recipes, SOPs, etc. in more realistic environment
- Continue to train on, maintain, and update SOPs
- Increase operational readiness and communication of changes to prepare operations on handling changes to control strategies and/or procedures
- Comprehensively testing code for new equipment prior to on-site qualification activities, saving roughly $1M or greater
- Test automation changes and updates offline before downloading to live environment

Test changes before implementation

As facilities run, changes must be made to keep production running as efficiently as possible. Many of these changes happen to occur in the control logic of the automation system. Applying the dynamic simulation model as a tool for risk assessment allows facilities to be "…assessing any new risks introduced by the change to define the strategy for maintaining compliance…" and to complete "evaluation of the change from the financial, technical (IT or engineering), and compliance perspectives at the lowest technically competent level…"[8].

Without a dynamic simulation model to test these changes offline, it is difficult to definitively define if a change is non-functional or functional. Testing automation changes against the dynamic simulation model allows facilities to decrease risk associated with online automation changes. By taking this additional step, facilities can further reduce the risk of patients' safety.

Improve SOPs

Standard Operating Procedures (SOPs) provide a standardized approach to a operating a process in documented form. For operators, SOPs define how to regulate the process during the shift. These are essential training resources and a key to running a productive facility.

As a facility gets upgraded, operations may shift, causing SOPs to become outdated. Testing old SOPs on a dynamic simulation makes it possible to understand the impacts the actions have on the process. This also creates an opportunity for an SOP to be updated when changes are made to the facility and tested on the offline dynamic simulation to evaluate the success of the revised SOP.

Sites that have used dynamic simulation for operator training have seen decreases in operator related incidents (3/4 incidents per year to none). Many sites have also experienced smoother batch execution because of their operator's familiarity on how to reset a batch when an upset occurs.

Value seen on past projects

Facilities that use dynamic simulation for capital projects and operational use see the highest level of value of this solution. A multi-purpose approach provides a cost-effective, consistent result, that maximizes the return on investment in the dynamic simulation model development.

Product and Process Understanding

Dynamic simulation provides the ability to review specifications for the control system. This application creates added value to complex processes: now control specifications can be scrutinized against a responsive process instead of a research laboratory or pilot plant. "An understanding of the supported process is fundamental to determining system requirements. Product and process understanding is the basis for making science and risk-based decisions to ensure that the system is fit for its intended use" (Page 19). Using dynamic simulation is also a critical piece of strategy when producing a new drug: by reducing the risk of not starting production on time, the drug product can be produced sooner, meaning it can get to patients to provide them the help they need.

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By following the guidance document Good Automated Manufacturing Practice (GAMP) 5 while utilizing dynamic simulation, pharmaceutical manufacturing facilities can use a comprehensive approach to improve patient safety, product quality, and data integrity. The dynamic simulation solution can be utilized for automation code projects, improvements, and training across many user platforms. This utilization allows for pharmaceutical manufacturing facilities to reduce their risk of not delivering drugs on time or safely, ultimately getting necessary drug product into the hands of patients in a shorter amount of time.

1 – Section 4.3, GAMP 5 A Risk-Based Approach to Compliant GxP Computerized Systems, Copyright ISPE 2008.
2 – Section 6.1.3, Ibid.
3 – Section 8.5.1, Ibid.
4 – Section 8.5.1, Ibid.
5 – Appendix M3, Section 3, Ibid.
6 – Section 5.4, Ibid.
7 – Appendix D5, Section 4.5, Ibid.
8 – Section 8.7, Ibid.

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