PAPERLESS MANUFACTURNG IN PHARAMACEUTICAL API

Whitepaper

Paperless Manufacturing in Pharmaceutical API

API (Active Pharmaceutical Ingredient) manufacturing, also known as primary manufacturing in the Life Sciences industry, poses a variety of unique challenges, when it comes to authoring of master batch records as well as recording and reviewing of executed batch records, especially in today's paper-based world. Following are some of the challenges faced:

1. During authoring, there is very little reusability of components as master recipes are always authored as a whole. Even though copy-and-paste features of word processing applications come in handy, they do very little to alleviate pains that arise due to lack of reusability. Further, versions of these master records have to be maintained manually and change control enforced procedurally, which entails a lot of paper going back and forth for review and signatures.

2. During execution, there is simply an enormous amount of manual activity that goes in to the manufacturing process, with very little repetition. Such a situation lends itself to a myriad of operator errors. Here are few of the most commonly noted problems.
    a. Once ERP releases a process order, the correct control recipe has to be issued to the shop floor and for this; the quality assurance department has to verify the printed copy of the control recipe manually against the controlled copy of master recipe. Such manual verification needs to be done for every batch before manufacturing can start.

    b. Once verified and approved for execution, recipe parameters, e.g., temperature, time, etc., have to be transcribed manually from paper in to the underlying automation system screens (DCS) for every single operation that is run on a particular unit, e.g., solvent charging, agitation, and heating, in a reactor. Similarly, upon completion of each individual operation, reporting data from automation has to be transcribed back on to the paper batch record. Considering that the same unit can be operated with several permutations and combinations of smaller operations for different products, a simple start and stop of a machine is not enough. Each operation needs a start and stop and there could be several (around 15-20) such operations to be performed within a given unit, e.g., reactor.

    c. Line clearance is a highly manual process that uses logbook data scattered across the factory to make determination on suitability of equipment and production rooms. Rules for line clearance can get very complicated and can

API Challenges

- Monolithic recipes prevent modularization
- Manual activities during execution
- High probability of errors during review
- Non-integrated support functions

slow down the production activity in the plant, e.g., Is the last product the same as current? When was the equipment cleaned and what type of cleaning was performed? etc.

d. All materials moving from one unit to another have to be manually verified and all material-related financial transactions have to be manually transcribed from the batch record in to the ERP system, e.g., consumptions and receipts.

3. During review, due to the high probability of errors that can happen during execution, there is again a tremendous amount of manual activity that is required.

   a. Every signature, every place of data capture, and every instruction on every page, needs to be checked by the reviewer for missing entries.

   b. The batch record needs to be checked for missing pages.

   c. Every calculation within the batch has to be verified by the reviewer.

   d. In critical operations, underlying automation data needs to be checked for limit violations of certain parameters.

   e. Batch-on-hold events in the underlying automation system need to be reviewed.

   f. All ancillary documentation needs to be checked for completeness.

   g. All printed labels and reports need to be reviewed for correctness.

4. Supporting functions – Logbooks for various equipment entities need to be manually updated during execution of batch or during cleaning. This requires making two entries for each usage of equipment, once in the batch record and once in the logbook. Failure to do so or recording of erroneous data, e.g., wrong date, could result in very serious compliance-related concerns.

The above situation gets even more complex in a generic-drugs manufacturing facility wherein multiple products are manufactured in the same facility using the same equipment and product changeover rate is very high due to limited exclusivity, if any, for a single pharmaceutical company. This means the entire cycle noted above is changing frequently in a generic-drug manufacturing plant as newer and newer drug products are introduced in to the market quite frequently. Result: heavy load of manual activity throughout the recipe lifecycle leading to errors in execution and recording of batches.

Additional Generic Facility Challenges

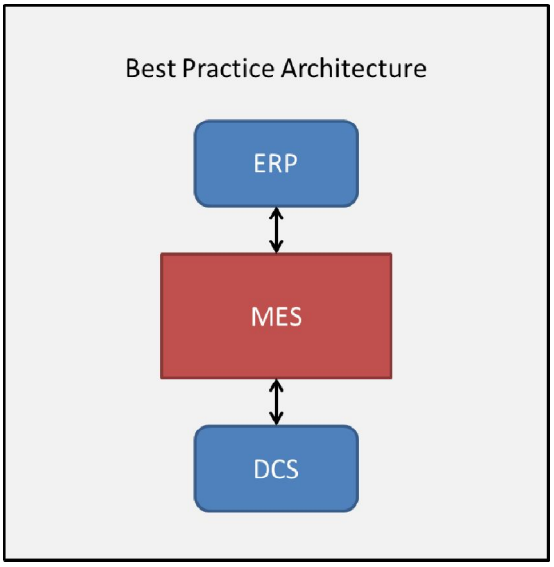
- Frequent changeovers
- Rate of new product introductions (NPI)
- Increased level of recipe authoring activities

Based on the above stated observations, at a typical API facility that does batch recording on paper, in summary, the following are key issues that need to be addressed.

1. Simplicity to be brought in to recipe authoring by increasing re-usability of validated sub-components, e.g., operations.
2. Manual entries to be minimized during production.
3. Transcription of data to be minimized (eliminated altogether wherever possible).
4. Order released in ERP to be available for execution on shop floor without requiring manual intervention/approval.
5. Sequence of process steps to be enforced and signatures and data entry to be enforced at every step.
6. Calculations to be automated.
7. Conditional processing to be automated either based on process parameter values or simple operator decisions.
8. Paper to be eliminated from the shop floor.
9. Manual entry of logbooks to be eliminated.
10. Manual method to determine suitability of equipment (line clearance) in production to be eliminated.
11. Manual method to determine suitability of materials in production to be eliminated.
12. Manual entry of material-related financial transactions in ERP to be eliminated.
13. Only true deviations to require manual review.

From the symptoms and issues listed above, it is obvious that some form of electronic information system would be required to bring about automation of processes and in doing so, take compliance to the next level. Such a system that focuses on the manufacturing process and fills the white space between ERP and automation is generally referred to as Manufacturing Execution System (MES). It is a system that could alleviate almost all of the above concerns and could streamline the entire drug manufacturing operation, right from dispensing to pack-out of final product. However, having a system alone may not be enough. The control philosophy between ERP, MES, and machine automation, needs to be carefully designed. It is very rare that manufacturers take full advantage of the end-to-end integration possibilities.

We start with the broader goal of having a single system for recipe authoring [MES], a single system for recipe execution [MES], a single system for batch review [MES], and a single system for machine-level automation [DCS].



The very basic operations that run the batch are defined in the underlying automation system (DCS), e.g., temperature control, solvent addition, agitation, etc. Below is an example of such an operation – material transfer – in the DCS.

20.2.1	Acquire control of the reactor.
20.2.2	Acquire safe state.
20.2.3	Operator Prompt: Close all the bottom manual valves of the reactor and confirm.
20.2.4	Operator prompt: Close the mobile vessel charging manual valve, discharge valve & confirm.
20.2.5	Operator Prompt: Connect mobile vessel vent to the vent header by hose pipe and confirm.
20.2.6	Operator prompt: Open the reactor bottom manual valve connected to mobile tank.
20.2.7	Set REACTOR_CHARGING_EM=S7.
20.2.8	Operator Prompt: Check for the line leakage and confirm YES or NO.
20.2.9	Set REACTOR_CHARGING_EM=S1
20.2.10	If Leak is yes arrest the leak and go to step **10**, else directly go to step**14**.
20.2.11	Operator Prompt: Open the mobile vessel vent valve and confirm.
20.2.12	Record initial pressure reading of **PT 501= P1**Kg/Cm2
20.2.13	Set PT 501 =P2 Kg/cm2
20.2.14	Set REACTOR_VENT_EM=S3.
20.2.15	Wait till PT501>=P2 Kg/Cm2.
20.2.16	Open sending reactor's bottom valve XV401.
20.2.17	Operator prompt: Observe Whether Mobile tank is filled to the desired level and confirm
20.2.18	CLOSE XV401.
20.2.19	Set REACTOR_VENT_EM=S1.
20.2.20	Set REACTOR_CHARGING_EM=S7 for **5 seconds**.
20.2.21	Set REACTOR_CHARGING_EM=S1.
20.2.22	Operator prompt: Close the charging valve and vent valve of the mobile tank and confirm.
20.2.23	Operator prompt: Disconnect the hose pipes from the mobile tank and confirm.
20.2.24	Operator prompt: Require transferring further?? YES or NO.
20.2.25	If YES go to step **4**, else go to step **31.**
20.2.26	Function Complete.

In the above figure, the red steps are manual steps where either the operator executes a work instruction or provides a response, e.g., Yes/No. The DCS contains the necessary ladder logic required to execute such modular operations, which form the least common denominators for master recipes. In order for the DCS to execute the ladder logic certain

parameter inputs are expected at runtime, e.g., temperature and time for temperature control operation, quantity for solvent addition operation, speed for agitation operation, etc. Once all the operations along with their parameters are defined and approved/released in the DCS, they are imported in to the MES – name of operation, name of each parameter, engineering unit of each parameter, design limits of each parameter, etc. These imported operations then form the basis for recipe authoring. In the MES, the recipe for a given unit (unit procedure) is put together using various permutations and combinations of such imported operations. The parameter values (set points) are then defined for each operation within the MES during recipe authoring.

At runtime, the MES runs the recipe operations by communicating with the DCS in the following way.

1. The MES selects the pre-defined unit and performs line clearance checks on the unit, e.g., Is the unit clean? Is the last product different from the current product? Is the unit being blocked by another process, etc? The unit is acquired only if checks pass.

2. The MES downloads the pre-defined control recipe (operation) along with all parameters to the DCS and starts the operation. Note that parameters values can be overwritten by creating deviations before start of operation – with e-signature – that can be tracked in the batch record.

3. The MES displays operator prompts encountered by the DCS during its execution, e.g., open bottom valve, perform visual check, etc. When a prompt is required (work instruction or a decision seeking an operator response), it is displayed in the MES as a pop-up that the user can interact with. This way, the operator is only viewing one screen (MES) and does not need to toggle between systems.

4. If the DCS places a batch on hold, MES pulls the condition and creates a deviation – with an e-signature – that can be tracked in the batch record. The MES also allows the operator to restart the held batch in the DCS, only after the underlying problem is addressed.

5. When the DCS parameters go out of limit, the MES captures such conditions as deviations – with e-signatures – that can be tracked in the batch record.

6. It is also possible for MES to place a batch in the DCS on hold, abort the batch, or disconnect with the DCS operation.

7. For all units used within the production recipe, the MES writes all relevant equipment information to the equipment logbook.

In addition to the above DCS-specific activities and communication, the following other production activities are carried out by the MES.

1. Dispensing: The MES provides a structured dispensing workflow wherein the system integrates with scales, identifies and verifies ERP raw materials by scanning barcodes, and prints labels for dispensed materials to ensure that they move to the right operation in the manufacturing process.

2. Material inputs: Solids and liquids that are dispensed in to drums, IBCs, mobile vessels, etc., for the process order are required to be identified using barcode scanning at certain points in the batch record. The MES ensures that the right materials are consumed in the right unit procedures for the right orders, and that unexpected materials are rejected.

3. Material outputs: The MES prints bar-coded labels for the materials produced by a unit (either transferred to the next unit or back to the warehouse).

4. Work instructions: The MES displays all basic work instructions that the operator needs to perform in the production process.

5. Calculations: The MES performs any numeric calculations or enables simple information flow from one place to another in the batch record.

In addition to the above, the MES can also be used to carry out warehouse-specific activities. The warehouse can be handled by MES in varying extents.

1. Automation of solvent flow from road tanker to bulk tanks, from bulk tank to day tanks, from day tank to mobile vessels, etc., as this information is critical to batch genealogy.

2. Complete replacement of the ERP system and becoming the sole system for operating the warehouse (this will include item 1 above).

MESTECH Services Private Limited

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We focus on Technology Consulting and Software Implementation for managing Manufacturing Operations. We have been successfully delivering technology consulting services to Automotive and Life Sciences majors with focus around implementing Manufacturing Execution Systems. We execute projects from concept to completion, wherein we start with requirements gathering and end with commissioning the system onsite, followed by support. Furthermore, we specialize in Rockwell Automation's MES solutions (PMX, FTPC, FTPS) that are based on their FactoryTalk platform.

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