Coating Line Operations for the Production of Drug-Containing Transdermal Patches

Kenneth C. Glade
LTS Lohmann Therapy Systems

Author Note
Kenneth C. Glade, Director of Engineering, LTS Lohmann Therapy Systems
21 Henderson Drive, West Caldwell, NJ 07006
Kenneth.glade@lts-corp.com
Abstract
What does the operation of a coating line look like in a GMP regulated world? For the newcomer to GMP production, a review of the FDA regulations that apply to medical and pharmaceutical products often leaves the newcomer with more questions than answers. Rather than providing a top-down analysis of the regulations, this paper presents a real-world example of the production of a typical coated web batch under GMP conditions to ensure its safety, integrity, strength, purity and quality. General requirements for proper documentation will be presented including logbooks, SOP’s, batch records, change controls and deviation management.

Keywords: coating, GMP, transdermal patches
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All drug products produced in the United States are subject to the Food and Drug Administration (FDA) laws known as Good Manufacturing Practices (GMPs). These apply to coated webs if the webs contain active drug ingredients or become parts of a drug delivery system. This paper outlines the main requirements that a coating company must follow to be compliant. Many examples will be provided to illustrate what compliance looks like, along with references to the relevant sections of the law. Although setting up a GMP-compliant coating operation is time-consuming and expensive, it provides a competitive advantage. Each year the requirements get harder and harder to meet, so the earlier the start, the better; and the longer the company maintains its GMP rating, the greater the barrier to entry for its competitors. The general operation of the coating line is not affected by the GMP requirements, but the consistency with which the coating line is operated, and the documented evidence of that consistency, are the key points for regulatory compliance.

Background

The following paragraphs define the scope of this paper and define some key terms. This paper assumes that the reader has a working knowledge of web coating equipment and materials.

Transdermal Patch

A transdermal patch is a way to deliver a drug dosage through the skin rather than by ingestion, injection, inhalation, or other means. For the purposes of this paper, a transdermal patch consists of an adhesive drug solution coated onto a backing layer, laminated to a release liner. A transdermal patch provides benefits to the patient such as 1) bypassing the digestive system, which by design wants to remove drugs from whatever is ingested, and 2) providing a time release drug dosage not always possible with drugs delivered by injection. See Figure 1 for a typical transdermal patch construction.
Coating Method

Any coating method may be used to produce a transdermal patch provided the patch provides its clinically proven results in a repeatable way. The coating process typically includes the following steps (see Figure 2):

- unwinding the backing layer
- applying the adhesive drug coating to the backing layer
- drying the drug coating
- unwinding the release liner
- laminating the coated backing layer to the release liner
- winding the laminated webs
Figure 2: Typical Coating Process

Converting

The post-processing of the coated web into individually packaged transdermal patches and then putting the pouches into cartons is outside the scope of this paper but practices described in this paper for the coating operations are similar for the converting operations, too.

Current Good Manufacturing Practice (cGMP)

The Food and Drug Administration (FDA) publishes the cGMP requirements as part of the Code of Federal Regulations (CFR) and they are laws. Violators can go to jail. The FDA provides its CFRs on its website, fda.gov. This paper introduces many of the cGMP requirements in a general way without purporting to give legal advice. Certain important cGMP requirements are outside the scope of this paper but are extremely important to any coating company that wants to produce drug-containing products.

Consumers expect their medicines to be safe and effective. The cGMP requirements were developed so that consumers do not have to worry about or investigate themselves whether a medicine is safe and effective.

The cGMPs are relatively short (compared to tax codes, for example) and written so that the drug manufacturer has the responsibility to convince the FDA that it has applied the rules properly. The “c” in cGMP indicates that the practices will evolve to keep pace with advances in manufacturing equipment and processes.
The FDA considers transdermal patches to be combination medical devices. The main CFR’s that apply are the following:

- 21 CFR Part 210, Current Good Manufacturing Practice In Manufacturing, Processing, Packing, Or Holding Of Drugs; General
- 21 CFR Part 211, Current Good Manufacturing Practice For Finished Pharmaceuticals
- 21 CFR Part 820, Quality System Regulation
- 21 CFR Part 11, Electronic Records; Electronic Signatures

Part 210 contains an overview of the status and applicability of the cGMPs as well as definitions for some key terms used in Part 211.

Part 211 gets more specific, dealing with personnel, buildings and facilities, equipment, and the procedural controls, records and reports required when manufacturing drug products.

Part 820 deals with the wider scope of establishing a quality control system and includes document controls, purchasing controls, labeling controls and what to do when the product produced does not conform to its specifications.

Part 11 concerns how to handle electronic records used to substantiate batch results, to ensure that the records were produced in a traceable way that can not be altered without leaving an audit trail.

Throughout this paper references to the CFRs will appear as (Part.Chapter). For example, 211.63 refers to CFR Part 211, chapter 63.

**Batch Operations**

**Prerequisites**

Before the start of a cGMP batch many prerequisites need to be satisfied. There must be a Quality department responsible for accepting or rejecting all aspects of production (820.20). There must be a Validation department which created, executed and approved a Validation Master Plan for the site, for the equipment and for the product (820.70, 820.75). The Quality department must have put into place systems to qualify rooms and machines and further systems to make sure no changes are made to the qualified items without review and approval. The Quality department must have set up procedures to identify when there is a deviation from an established standard procedure, to investigate to determine its root cause, and to implement corrective and preventive actions (CAPAs) so that the deviation does not repeat.
Typically, these and similar systems are documented in Standard Operating Procedures (SOPs) which are themselves subject to change control. Documents subject to change control are commonly called controlled documents.

With these supervisory systems in place, the company can start hiring staff qualified according to their specific job requirements for education, training and experience (211.25). Training on the SOPs must be given and training records kept.

The rooms used for production must have a suitable design (211.42) with proper temperature and humidity (211.42), lighting (211.44) and air cleanliness (211.46). The rooms must be maintained in good working order (211.58). The rooms must be cleaned and cleaning records kept.

Equipment also must be suitable by design (211.63), free from features that could contaminate the products (211.65), maintained, calibrated, and cleaned (211.67). Records must be kept to provide documented proof.

Suitable design for a coating line would include features typically found in other clean room coating processes. These include:

1. Machine surfaces should be smooth, without surface features like unground welds that can be difficult to clean and capture drug ingredients that may contaminate later batches.

2. Machine surfaces that may contact the coated or uncoated side of the web should be made from materials that are non-reactive with the webs and coating solution components. This typically means stainless steel machine frames with chrome-plated coating rollers. Elastomer covered rollers should be coated with FDA approved elastomers.

3. Lubricants that may drip or leak onto the product, or may come into contact with the product due to excess or sloppy application, should be food grade (178.3570).

Note that these surface and lubricant requirements also apply to the solution preparation, storage and transportation equipment.

If there are any materials that come into contact with the finished product such as tubing, vessel gaskets, or packaging, for which there is any question about contamination due to migration of the material into the drug product, a study must be conducted to make sure that no such contamination occurs. This study is commonly called an Extractables and Leachables study.

A logbook with entries to record cleanings and uses of each machine must be kept (211.182).
There must be written procedures for the coating operations (211.22, 211.100) including a Master Batch Record (211.186) from which the Executed Batch Record (211.188) is created.

**Before coating the batch**

According to CGMPs the batch must be produced using the same materials, equipment and actions that are part of the approved (validated) process. There must be documented evidence of compliance.

Before the start of the coating batch, several things must have happened. A production planner prepares a Executed Batch Record from a controlled copy of the Master Batch Record. A Executed Batch Record for coating typically consists of 30 – 40 pages and several hundred places for data entry during the batch. Execution of each step of the batch requires two signatures: one by the person who performed the task, and one by the person who checked that the task was done properly. The Coating Supervisor will review and approve the Executed Batch Record after the batch is complete. Critical tasks may require the supervisor to sign also at the time the task was done.

The production planner checks that all required raw materials and intermediate goods (previously prepared drug-containing coating solution, previously coated webs) are available in sufficient quantities and that all QC testing has been completed on these materials. Then, the planner requests that the proper quantities of raw materials and intermediate goods be sent to the coating room. Part of the Executed Batch Record steps will be to verify that the proper materials are present at the coating line prior to starting the batch. This is done by scanning the bar code on each item and comparing the Bill of Materials with the scanned items.

The Executed Batch Record includes a description of each major piece of equipment used to produce the batch, e.g. coating line, pump, weigh scales, etc. (211.105). The coating operators will verify that the proper equipment is available and in good working condition. They also check the appropriate logbooks to make sure that the equipment was properly and recently maintained, calibrated and cleaned. A cleaning swab must be taken before the batch to make sure that there are no leftover traces of a previous product that might affect the current batch.

The operators also must confirm that the room environmental conditions match the requirements for the product. They check the appropriate logbooks for any temperature or humidity excursions that might affect the batch and ensure that the room conditions were brought into specification before the start the batch. They will check the room conditions periodically
during the batch, too, if these conditions are noted as critical in the batch record. Lastly, they check the room cleaning logbook to make sure that the room was recently and properly cleaned.

The Executed Batch Record also includes space to document any calculations made during the batch, e.g. converting web width from inches to mm in case the coating width adjustment is set using metric dimensions, but the incoming web is specified in English units.

Once the materials, equipment and room conditions have been confirmed and documented, the operators start setting up the coating line per the batch record requirements. The drying oven is brought to operating temperatures and airflows, auxiliary equipment like hydraulic power units or corona treaters are started, and the operators thread the line with web.

The operators manually adjust machine components like dampers and edge guide sensors if these are not automatically positioned. They enter setpoints from the batch record into the process controllers, and document that all critical process parameters are within batch record limits.

The operators also must challenge any automated defect detection systems to make sure poor quality product is marked for later rejection.

**During the batch**

As the operators begin the coating process, they will first establish the proper coating application and appearance. Exactly how this is done varies with the coating method and is outside the scope of this paper. The operators take coat weight samples at the start of coating, and periodically though the batch, to test and confirm that the coating is within specifications. The operators perform any other in-process-controls as required by the batch record.

The critical process parameters are monitored throughout the batch and recorded on a time or web length basis to provide the documented evidence that the process remained in control throughout the batch. The documentation may be via hand-written forms or electronic data collection, or by a combination of the two. If done electronically, the capturing system must comply with 21 CFR Part 11.

If all does well, the batch concludes when the desired linear length of coated web has been produced. In this case, the operators begin the batch closeout process as described in the “After the batch” section below.

If something doesn’t go as expected, the operators follow the SOP for process deviations. This includes flagging the portion of the coated web affected by whatever was observed and
creating a deviation notice with all the supporting details and observations noted. The operators send the deviation notice to the Quality Assurance department, which beings a formal investigation to determine the impact of the observation on the quality of the product produced, the root cause of the unexpected observation, and any corrective and preventive actions developed to eliminate the recurrence of the same unexpected observation in any future batches.

Depending on the requirements for the drug product being produced, it may be necessary to account for the amount of the active ingredient that was actually coated and not scrapped. This is a sort of yield calculation but limited to the drug ingredients. To calculate this yield it may be necessary to accurately weigh the coating solution vessel before and after the batch, and the coated rolls before and after, and any coated and uncoated web that is scrapped, so that the precise amount of solution can be known. There are special requirements for balances used to perform these weight operations to ensure consistent accuracy. [USP chapter 41]

**After the batch**

Once the desired amount of coated web has been produced, the operators can finish the batch. Besides the steps necessary to properly shut down the coating line, there are several requirements to close the Executed Batch Record.

The operators perform additional record-keeping actions as required in the Executed Batch Record. These might include documenting the exact date and time of batch finish, which is used as a check that the batch production time was within established limits (CFR 211.11) and in a later step to verify that the amount of coated web produced (line speed x time) matches the amount of web and coating solution consumed. The yield must be within established limits (CFR 211.103).

Typically, there are other batch closeout calculations, for example, converting coat weight samples from the raw units of measurement (g/cm2) to a standard (g/m2). Such calculations may be performed and documented using validated spreadsheets, or they may be calculated manually with each step in the calculation recorded in the batch record.

Another typical batch closeout step would be to document that amount of each web and material that is leftover. This helps with inventory control as well as with the yield calculations.

The operators cover the finished product typically by placing each roll in an opaqu plastic bag to shield it against physical or light contamination. Then, they send the bagged rolls to the proper storage location.
The operators perform a line clearance and cleaning to make sure that there is no leftover web or coating solution left on the coating line that may contaminate the next batch. This is done even if the next batch will be of the same drug product, so that there is traceability of which lots of raw materials were used to produce each batch.

The coating supervisor reviews each entry in the Executed Batch Record, checking for proper execution of the batch steps and for proper documented evidence for the batch. The operating crew must follow Good Documentation Practices (GDP) when preparing all documents. Although GDP is outside the scope of this paper, its requirements include legible hand writing, and no writing over or erasing entries. If the supervisor finds any GDP violations, they can correct the entry with a proper annotation.

Production Record Review and Batch Release Testing.

The rolls just produced are kept in a quarantine status until the Quality Unit performs an overall review of the production batch records and supporting documents (211.12), the Quality Control department performs the required tests on samples taken during and after coating, and the Quality Assurance team reviews the all the records and officially releases the batch (211.165).

Conclusion

Compliance with cGMP regulations contains many components but need not be overwhelming. The FDA publishes guidelines for compliance, though the proof of adequate compliance belongs to the coating company. Each step of the production must follow the relevant sections of the CFRs and provide documented evidence that the steps were correctly followed. Most of the work happens before the first batch is coated, providing a competitive advantage for the coating company that has successfully overcome this barrier to entry.