U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Drugs

Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Records and Reports

1. Some products, such as transdermal patches, are made using manufacturing processes with higher in-process material reject rates than for other products and processes. Is this okay?

Maybe. It depends on the cause and consistency of the reject rate. Many transdermal patch manufacturing processes produce more waste (i.e., lower yield from theoretical) than other pharmaceutical processes. This should not of itself be a concern. The waste is usually due to the cumulative effect of roll splicing, line start-ups and stoppages, roll-stock changes, and perhaps higher rates of in-process sampling. This is most pronounced for processes involving lamination of rolls of various component layers. Roll-stock defects detected during adhesive coating of the roll, for example, can often only be rejected from the roll after final fabrication/lamination of the entire patch, which contributes to the final process waste stream.

We expect that validated and well-controlled processes will achieve fairly consistent waste amounts batch-to-batch. Waste in excess of the normal operating rates may need (see 211.192) to be evaluated to determine cause (e.g., due to increase in sampling or higher than normal component defects... or both) and the consequences on product quality assessed. We've seen a small number of cases where unusually high intra-batch rejects/losses were due to excessive component quality variability and poorly developed processes.

References:

- 21 CFR 211.100: Written procedures; deviations
- 21 CFR 211.103: Calculation of yield
- 21 CFR 211.110: Sampling and testing of in-process materials and drug products
- 21 CFR 211.192: Production record review

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2. Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?

The CGMP regulations (21 CFR 210 and 211) for finished pharmaceutical manufacturing do not specifically address the requirement to conduct, or to keep records of, internal quality assurance audits. If the report in question were from a routine audit to verify that the firm's quality system is operating as intended, then it would be acceptable if the firm elected to discard the report once all corrections have been verified.

However, any documentation of corrective action as a result of such an audit would have to be retained (see 211.180 and 211.188). For example, if a routine internal audit finds a problem with a mixing step and the outcome is a change in mixing time, all affected procedures, including the master production record, are to reflect the necessary changes, and such records are subject to FDA inspection as usual. Any investigation into the impact this problem had on related batches is to be retained and also made available for inspection by FDA (see 211.192).

In addition, any reports of investigations or evaluations prepared in response to, for example, a product complaint (211.198), vendor qualification (211.84), periodic review of records and data (211.180(e)), and a failure investigation (211.192) are not internal audits as discussed above. Such records are subject to FDA inspection and must be retained for at least the time specified in the CGMP regulations (see 211.180).

References:

- Preamble to the *Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding* regulations; Federal Register, September 29, 1978 (vol. 43, no. 190), page 45015, paragraph 4 http://www.fda.gov/cder/dmpq
- 21 CFR 211.84: Testing and approval/rejection of components, drug product containers, and closures
- 21 CFR 211.180: General requirements
- 21 CFR 211.192: Production record review
- 21 CFR 211.198: Complaint files
- Compliance Policy Guide Sec. 130-300, (7151.02) http://www.fda.gov/ora/compliance_ref/cpg/cpggenl/cpg130-300.html

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3.How do the Part 11 regulations and "predicate rule requirements" (in 21 CFR Part 211) apply to the electronic records created by computerized laboratory systems and the associated printed chromatograms that are used in drug manufacturing and testing?

Some in industry misinterpret the following text from "The Guidance for Industry – Part 11, Electronic Records; Electronic Signatures – Scope and Application" (Part 11 Guidance; lines 164 to 171) to mean that in all cases paper printouts of electronic records satisfy predicate rule requirements in 21 CFR Part 211.

> "Under the narrow interpretation of the scope of part 11, with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be 'using electronic records in lieu of paper records' under §§ 11.2(a) and 11.2(b). In these instances, the use of computer systems in the generation of paper records would not trigger part 11."

The Part 11 Guidance also states (in lines 150-152), that:

> "…persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules."

For High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) systems (and other computerized systems involving user inputs, outputs, audit trials, etc.), the predicate rules, such as 21 CFR 211.68 and 21 CFR 211.180(d), require the electronic records themselves to be retained and maintained in accordance with those regulations. 21 CFR 211.180(d) requires records to be retained "either as original records or true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records." 21 CFR 211.68 further states that: "[H]ard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained" (emphasis added). The printed paper copy of the chromatogram would not be considered a "true copy" of the entire electronic raw data used to create that chromatogram, as required by 21 CFR 211.180(d). The printed chromatogram would also not be considered an "exact and complete" copy of the electronic raw data used to create the chromatogram, as required by 21 CFR 211.68. The chromatogram does not generally include, for example, the injection sequence, instrument method, integration method, or the audit trail, of which all were used to create the chromatogram or are associated with its validity. Therefore, the printed chromatograms used in drug manufacturing and testing do not satisfy the predicate rule requirements in 21 CFR Part 211. The electronic records created by the computerized laboratory systems must be maintained under these requirements.

We recognize that there are cases where it could be appropriate for the printed chromatogram to be used within laboratories for the review of test results. Similarly, it also may be acceptable to provide the printed chromatogram during a regulatory inspection or for application review purposes. However, the electronic record must be maintained and readily available for review by, for example, QC/QA personnel or the FDA investigator.

In summary, decisions on how to maintain records for computerized systems should be based on predicate rule requirements. We recommend that these decisions be supported by a sound risk assessment.

References:

- Guidance for Industry – Part 11, Electronic Records; Electronic Signatures – Scope and Application (http://www.fda.gov/cder/guidance/5667fnl.pdf)
- 21 CFR 211.180(d): General Requirements
- 21 CFR 211.68: Automatic, Mechanical, and Electronic Equipment

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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm
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4. How does the FDA interpret the regulations (21 CFR Part 211) regarding the establishment of expiry dating for chemicals, reagents, solutions, and solvents?

Laboratory "reagents, and standard solutions," as referenced in the CGMP regulations at 211.194, includes laboratory chemicals such as solvents (including mobile phases), dry chemicals (salts, primary standards, etc.), and solutions (buffers, acids/bases, quantitative analytical preparations, etc.), whether purchased or prepared in-house. Laboratory reagents and solutions are used in analytical tests of components, in-process materials, and finished products.

If the purchased laboratory reagent or solution includes a manufacturer's suggested "use by" or expiry date, that date should be followed. For purchased laboratory reagents and solutions without a "use by" or expiry date, FDA would expect that an assessment be conducted (literature review may be acceptable) of that specific chemical's or chemical family's stability and that an appropriate "use by" or expiry date be determined.

For in-house prepared solutions, such as mobile phases or other non-quantitative solutions, FDA would expect that an assessment be conducted (again, literature review may be acceptable) to determine an appropriate expiry period. However, for in-house prepared solutions used for quantitative analysis, such as sample or standard solutions used in assay or impurity testing or titration solutions, FDA requires that formal stability studies be conducted to determine an appropriate expiry. As mentioned in *Guidance for Industry: Q2B Validation of Analytical Procedures: Methodology,* the stability of analytical solutions is a typical method variation that should be evaluated during robustness testing during method validation. Method validation is a CGMP requirement at 211.160(b).

The determined "use by" or expiry dates should be documented within a procedure and followed. Procedures for any in-house prepared laboratory solution should include the determined stability timeframe, and should instruct that these solutions be labeled with the appropriately determined "use by" or expiration date upon preparation and discarded upon expiration.

These principles would also apply to API manufacturing and testing sites. The use of "reagents and solutions" and "use by" dates are found throughout *Guidance for Industry: Q7, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*.

References:

- FDA Current Good Manufacturing Practice for Finished Pharmaceuticals regulations at 21 CFR 211.160 and 211.194
  - 211.160 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.160
  - 211.194 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.194
- FDA Guidance for Industry
  - ICH Q7, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Section 11, Laboratory Controls http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf
  - ICH Q2B, Validation of Analytical Procedures: Methodology http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073384.pdf

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