Batch Record Review Overview

Ground Rules

- Please put your cell phones on vibrate.
- Actively participate and ask questions freely. This will help you learn.
- You must be in attendance for the entire training session to receive credit.
- Offer any pertinent situations/examples that have arisen in your work area or from past work experience.
- Issues/questions that cannot be resolved/answered during this program will be placed in a “Parking Lot”.

Batch Record Review Overview Training

- Segment #1: Batch Record Review General Information
- Segment #2: What do the Regulations Say?
- Segment #3: Good Documentation Practice Review
- Segment #4: Batch Record Content Verification
- Segment #5: Issue Resolution
- Segment #6: Final Review and Disposition

Learning Segment #1

Batch Record Review General Information

WHAT is a Batch Record?

- Written history of a specific product produced by a given company.
  - Manufacture
  - Packaging
  - Labeling
  - Testing
  - Review of
- Record involves:
  - Actions of individuals
  - Signatures
  - Test results
  - Product labels
  - Any atypical results
  - Review and approvals by Quality Department
  - Documentation of disposition of product from specific batch

WHAT is Included in a Batch Record?

- Date of activity
- List of materials
- Measurements
- Equipment used
- Equipment calibrations current
- In-process and control results
- Identity of individuals
- Accountability calculations
- Sampling activities
- Packaging and labeling inspections
- Process Issue/Variance
- In-Process, Control and Finished Goods Test Results
- Disposition of product (acceptance or rejection)

A Note about Terminology…

For Manufacturing:

- New format Manufacturing Records use the term "Accountability".

For Packaging:

- The Packaging Group 'reconciles labels and components'.
- There is a new format for Packaging Records.
- Packaging Records provide 'Accountability Forms", which determine finished product 'yields' (for example: 22,332 bottles).

WHAT Types of Batch Records Exist?

- Active Pharmaceutical Ingredient (API)
- Bulk drug manufacturing
- Finished product manufacturing
- Labeling and packaging

WHAT is Batch Record Review?

- Batch Production Records (BPRs) – reviewed by manufacturing and packaging before received by QA for review.
- QA Inspection Documents – reviewed by QA Inspection Group before received by QA for review.
- Types of reviews completed during BPR review:
  - Good Documentation Practices
  - Key Components of the Batch Production Record
  - Process Steps
  - Source Data or original data
  - Calculations
  - Process Issue/Variance
  - Calibration of Equipment, if applicable
  - Expiration of Consumables
  - Room and Equipment Cleaning and Clearance, if applicable
  - Material, Sample and Reject Accountability

WHY Batch Records are Reviewed?

Batch Record Review Forms a Critical Component of cGMP:

- cGMP are regulations which are enforceable by law
- The purpose of cGMP is to protect the public's health
- Approved procedures must be followed
- All activities must be documented upon completion of process steps in a batch record

WHO Reviews Batch Records

- Batch Production Records must be reviewed and approved by qualified individual(s), including:
  - Manufacturing
  - Packaging Records by Packaging
  - Quality Assurance

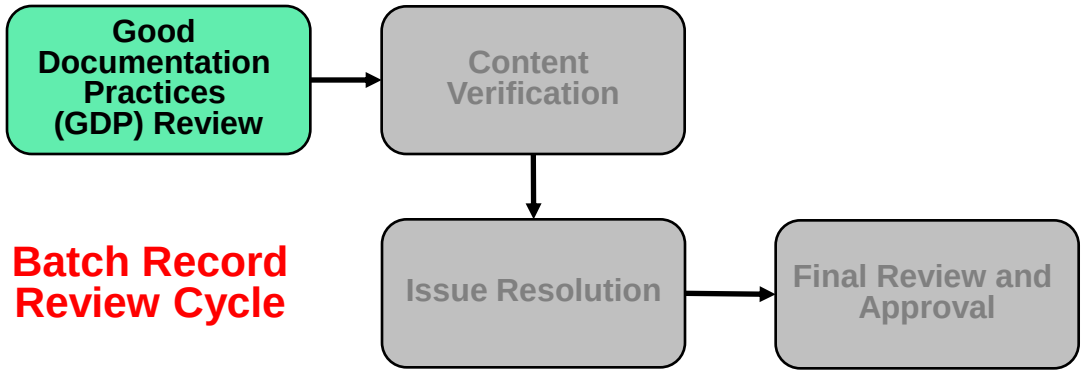
Learning Segment #2

What Do The Regulations Say?

Code of Federal Regulations

21CFR211.192 states:

"All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed."

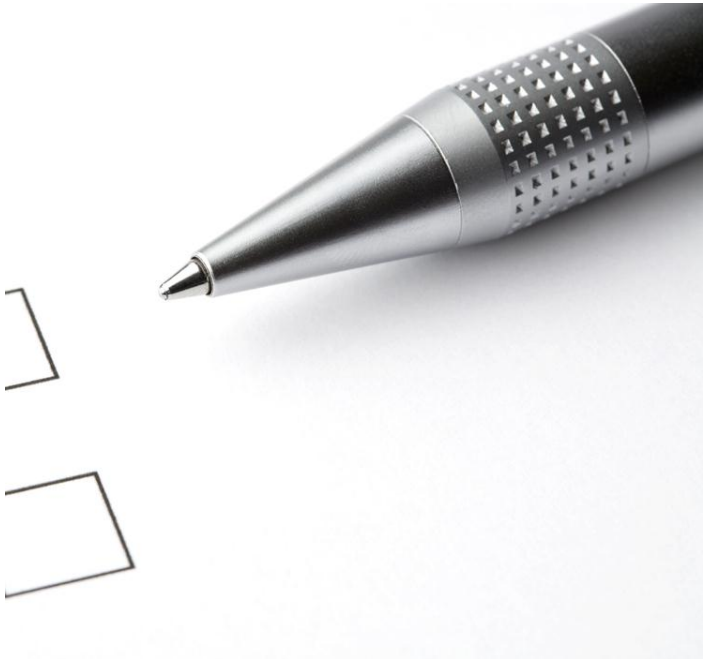


Learning Segment #3

Good Documentation Practice Review

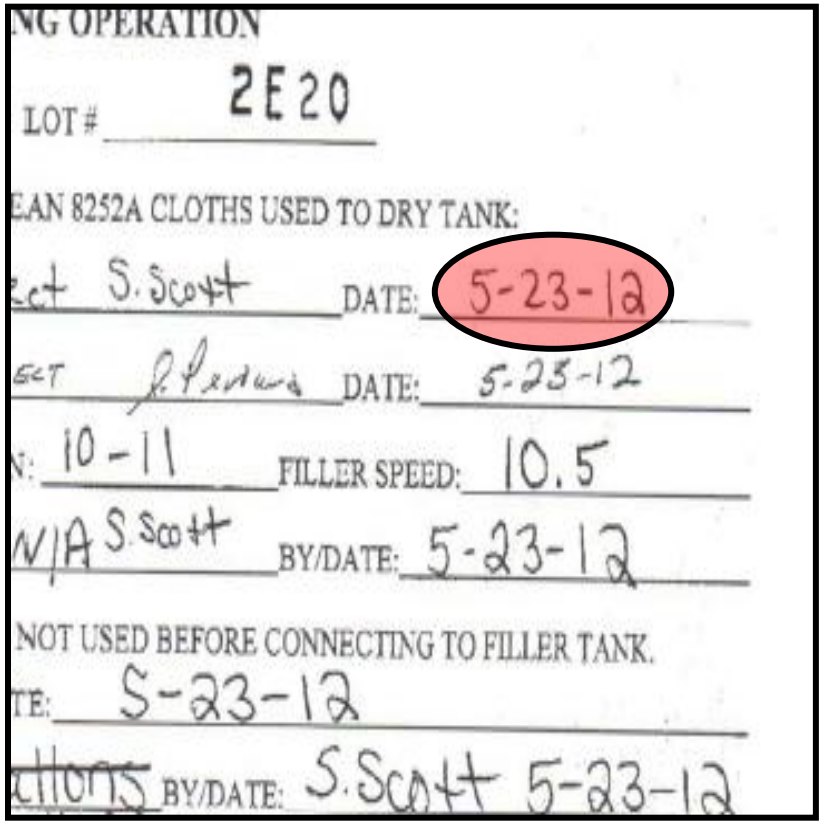
Ink Requirements

- Appropriate ink practices:
  - Permanent (indelible) black ink
  - Red ink where specified
  - Ball-point pen
- Inappropriate ink practices:
  - Pencils
  - Erasable Ink
  - Highlighters
  - Dry Erase Markers
  - Gels
  - Red Ink



Formatting Dates

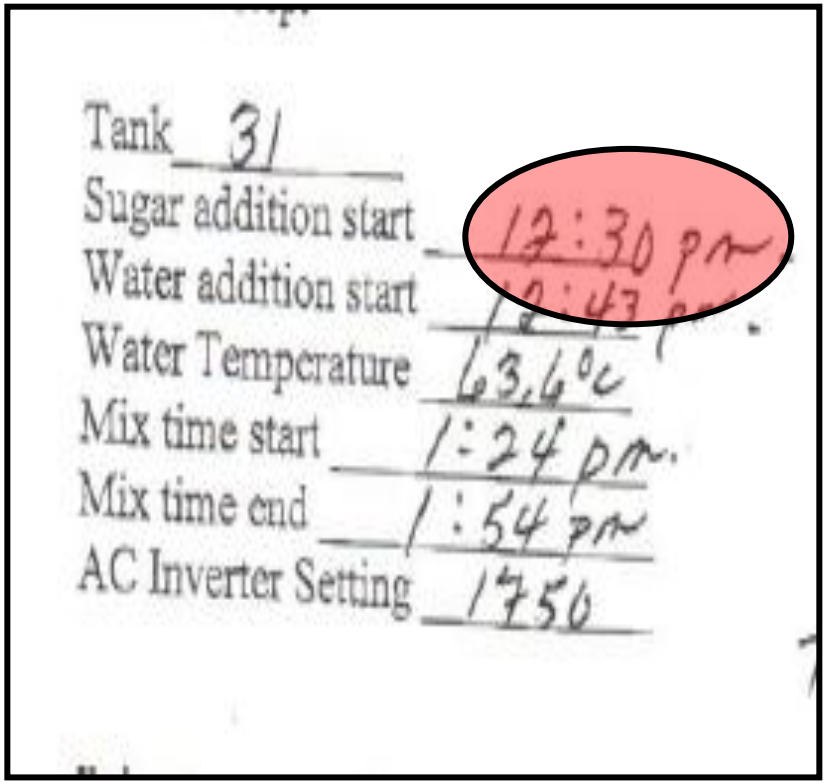
- Record dates following common U.S. practice
  - Month/day/year
  - Month-day-year
- Example – September 1, 2005 written:
  - 9/1/05
  - 9-1-05
  - 09/01/05
  - 09-01-05
  - 09-01-2005
  - 09/01/2005



Formatting Dates

Documenting Time

- Record time in AM/PM format.
- Date and times in sequential order
- Do NOT backdate.
- Date/time not captured in real time:
  - Write correct date task was performed
  - Note explaining why it was not captured
  - Initial and date the entry
- Ensure elapsed time:
  - Calculated correctly.
  - Meets specifications applicable batch production record
- Rounding (when permitted):
  - When minutes or seconds are greater than 30, round up
  - When minutes or seconds are less than 30, round down



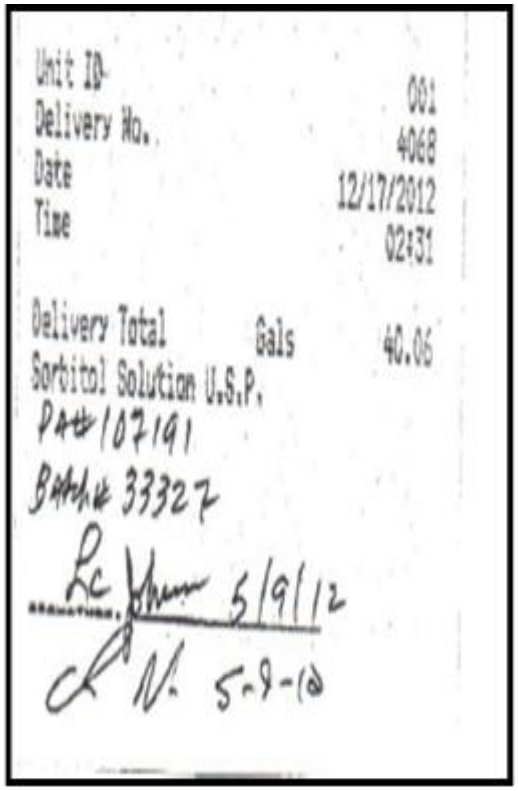
Documenting Time

Documenting Signature Requirements

Roles	Role Definition
Performer	Performs the task according to a procedure. Source data such as an unused pallet tag that is placed into the batch record required an explanation as to why it has been placed into the batch record. Signature/initial and date is needed. **Note:** Signature/Initial and Date should be included when making any entry in the batch record that is “undefined space” or in addition to other data documented in defined spaces.
Verifier	Performs a physical examination of the work ✓ Repeats Calculations ✓ Reviews labels and/or Source Documents for accuracy and completeness ✓ Ensures that data is correct, complete, and properly recorded. ✓ Checks initials vs a personal signature list to confirm that everyone that has signed the record has also signed/date the personnel list
Approver	Ensures that: ✓ Appropriate personnel verified the work ✓ Tasks were completed according to the appropriate procedure and documentation of the task is complete and acceptable from a technical and compliance perspective.

Dealing with Raw Data

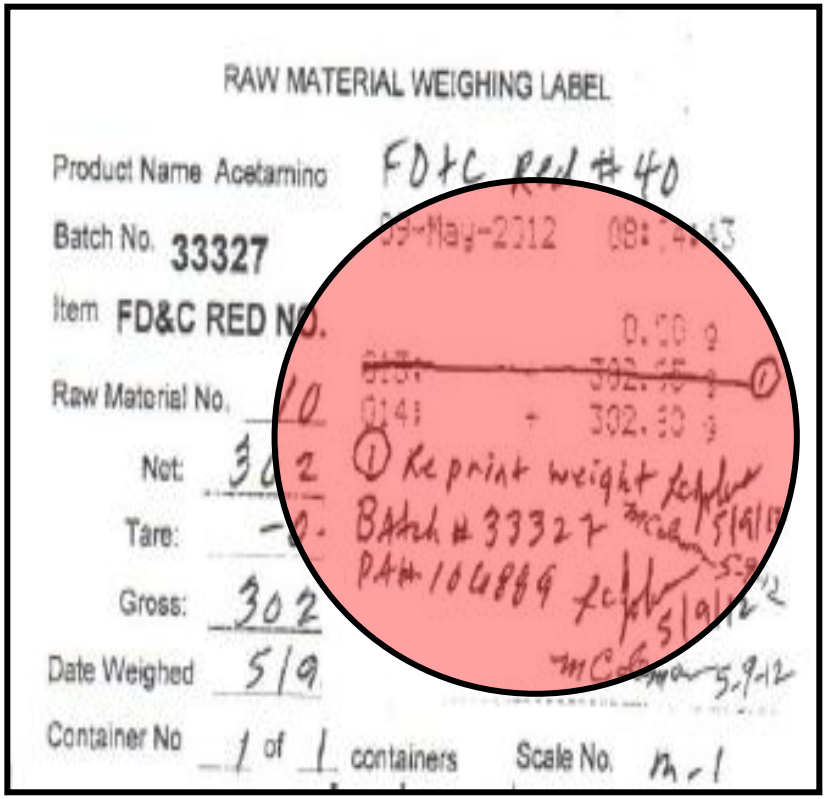
- Data collected from a source which has not been subjected to processing or other manipulation.
- Used to reconstruct and evaluate original observation or event.
- Attached to batch record.
- Examples:
  - Test Results
  - Assay (test) Data
  - Verification of an Operation
  - Mathematical Calculations
  - Equipment Print Outs
  - Lab Data



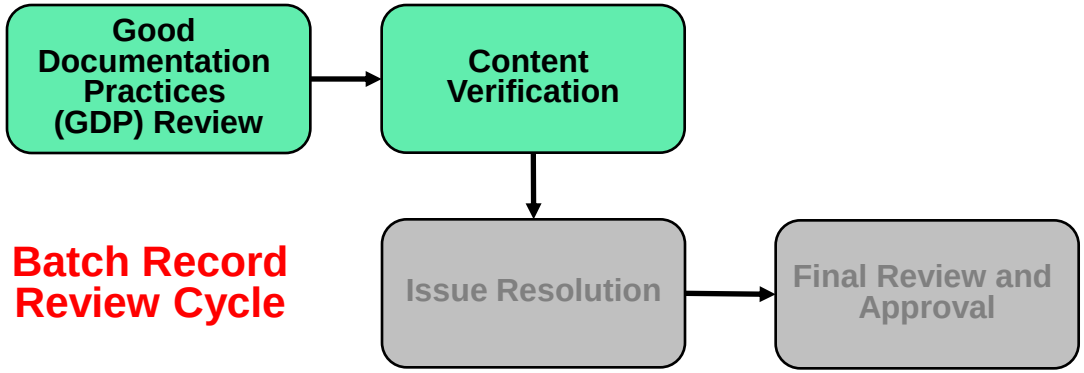
Example of Raw Data Attached

Corrections

- Cross-outs - single line through incorrect data (data still legible).
  - Third person initial and date cross out.
  - Multiple cross-outs – reviewer ensure correction comments are clearly linked to associated cross-out.
- Real-Time Entries.
  - If a shift ends and then begins on the same day, a correction should be clear that it is from a different shift.
- Explanations.
  - If needed.
  - Provide an explanation including how the correction was verified.
- Document/Notes – do not use scraps of paper or post it notes.



Example of Correction



Learning Segment #4

Batch Record Content Verification

Key Components

- All pages present and current batch record was used per the manufacturing or packaging process being executed.
- Each page includes (at a minimum) Product Name and batch or lot number.
- All pages are present and sequential.
- Lot Number is consistent throughout record – batch or lot number for bulk manufacturing and manufacturing lot number for packaging.
- Entries neat and legible.

<table>
<tr><td colspan="3">Acme Pharmaceuticals, Inc.

Batch Production Record</td><td>ACME
Pharmaceuticals</td></tr>
<tr><td colspan="2">Product: Sodium Phosphate

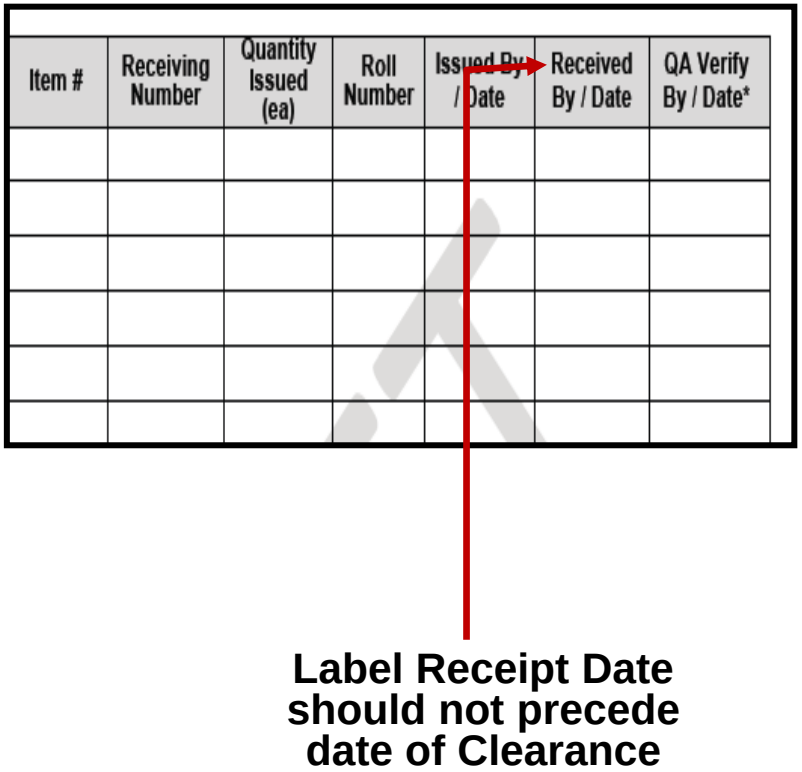
Oral Solution (10 mg Prednisome 5 mL)</td><td>Batch No.</td><td>Lot No.</td></tr>
<tr><td>Formula No. 0789

ANDA #76-920</td><td>Batch Size:

1000 Gal</td><td>Effective Date:</td><td>Revision No: 05</td></tr>
</table>

Process Steps

- Chronological order and/or simultaneous processes in logical order.
- Allows for easy identification of missing parts and inconsistent/incomplete operations or errors.
- Verifying operations documented in BPR were performed chronologically – examples:
  - Date labeling is received to Line should not precede date of Clearance.
  - Date of Finished Product Reconciliation should not occur prior to end of Packaging run.
  - Expiration date entry on Raw Material Table should not occur prior to date when raw materials are weighed.



Source Data

- Verify:
  - Information transcribed from a previous step (original source) or another BPR is accurate.
  - Document being used is valid.
  - Transcribed data is from original source data.

    If transcribed data is from another BPR, verify against original entry.

Calculations

- Values obtained in calculations must be verified.
- Values often transcribed and used in additional calculations carried throughout process.
- Many different types of calculations during batch production record review.
  - Time
  - Date
  - Expiration
  - General mathematical
- Expiration Date calculations must be verified.

Checking Calculations

- Information from previous steps has been transcribed correctly prior to performing calculation.
- Calculations using a calculator or equivalent (excel) – full calculations should be shown.
- Check calculation/reading/parameter against operating ranges (or action limits) listed in BPR.
- Data recorded is in same significant digit format as specified in operating range.
- Values are followed by appropriate units of measure.

Process Issue/Variance

- Referenced in the BPR.
- Verify all necessary step details are provided.
- Correct steps affected by deviation are mentioned.
  - If affected step mentioned in Process Issue or Variance cannot be cited – reference it near an associated step in the batch production record, if possible.
- Multiple Process Issues or Variances referenced on one page – number each Process Issue or Variance and associated step.

Calibration of Equipment

- Verify all equipment used during manufacturing was in calibration at beginning of use.
  - Check date equipment was used.
  - Reference calibration due date recorded in batch production record or logbook.
- Use of equipment in manufacturing should occur prior to calibration due date.

Expiration of Consumables

- Examples of consumables:
  - Raw materials used to make solutions
  - Disposables
  - Bottles
  - Sterilized items
- Components (consumables) identified in batch production record cannot be expired at start of use.
- Check that consumed solutions or components are used within expiration dating period.
- Bill of Materials or Pick List.
  - Indicate what was used during manufacturing.
  - Used as a guide when verifying materials used.
- Batch-specific components or product-contact items must be prior to expiry.

Room/Equipment Cleaning & Clearance

- Verify room and equipment used in manufacturing process cleaned prior to use.
- Check for room/equipment cleaning:
  - Batch production record
  - Logbook entries (site dependent)
- Verify room/line cleared of products not related to the batch being manufactured.

Material, Sample & Reject Reconciliation & Accountability

- All materials, samples and rejects must be accounted for and reconciled in batch production record.
- Ensure that:
  - All samples taken according to item specification and/or batch production record, accounted for and properly documented.
  - Rejected materials are accounted for and documented appropriately.
- Verify all materials allotted to the batch :
  - Accounted for.
  - Any excess returned to inventory.
- Ensure process and final yields are within expected range.