Frederick National Laboratory for Cancer Research

BIOPHARMACEUTICAL DEVELOPMENT PROGRAM

SOP Title:	**Quality Assurance Review of Completed Batch Production Records and Other Manufacturing Production Records**
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1. PURPOSE

This SOP defines the procedure for review of completed Batch Production Records (BPR) for GMP, GLP, and non-GMP production and for the review of lab notebooks for GLP and non-GMP/GLP productions. Batch Production Records are issued per **SOP 21415** - Preparation, Issue, Completion, and Approval of Master Production Records.

2. SCOPE

This procedure applies to Biopharmaceutical Quality Assurance (BQA) personnel involved in reviewing BPRs and lab notebooks.

3. RESPONSIBILITIES

3.1 The Director, Biopharmaceutical Quality Assurance (BQA)

- Defines this procedure.

3.2 The Project Supervisor, BDP

- Reviews completed batch production record or lab notebooks for technical accuracy and correct completion prior to submission to BQA.

3.3 Biopharmaceutical Quality Assurance (BQA)

- Reviews for Compliance and disposition of completed batch production records and/or lab notebooks used to document manufacturing processes.

4. DEFINITIONS

- **Batch Production Record (BPR)** – A copy of the MPR to which a lot number has been printed that is used to directly capture manufacturing data and any supporting testing data or documentation required to complete the batch production record.
- **Lab Notebook** – Legal documents that provides a mechanism to capture critical information about experiments or processes that may be needed to reconstruct events at a later time (for example, as part of a CMC section in an IND), to serve as a foundation for future work, to transfer information from development to other departments or institutions, or to protect intellectual property.
- **Master Production Record (MPR)** – The master document containing detailed instructions for performance of a specific procedure. The document is used to record critical steps, parameters, raw data, etc. as events occur during the production of a product.

5. REVIEWING COMPLETED BATCH PRODUCTION RECORDS FOR CGMP PRODUCTION

5.1 Upon completion of a BPR, the BDP Project/Production Supervisor reviews the document and ensures that the BPR is complete, correct, and technically accurate, and returns the document to BQA.

5.2 Receipt of the completed BPR is entered in the batch record database.

5.3 BQA reviews the batch production record using the following guidelines and records the results on **Form 21103-01**, Batch Production Record Review Checklist.

5.3.1 Verify that the necessary pages have been included.

5.3.2 Verify that the BPR has a completed/approved Area Clearance from BQA.

5.3.3 Verify that the lot number is accurate.

5.3.4 Verify that the BPR contains a list of employees who performed the process, including unique signature and initials for each.

5.3.5 Verify that the Equipment and Material tables have been properly completed.

5.3.6 Verify that raw materials were used prior to expiration (where expiry is assigned) and that all entries are complete.

5.3.7 Verify that equipment used was within the calibration or certification expiration date.

5.3.8 Verify that weigh records are complete, properly labeled, and reflect the correct quantities needed per formulation requirements, are properly attached to the BPR, and initialed and dated.

5.3.9 Verify oven and autoclave records by reviewing the chart or printout to ensure that the correct temperature and time was attained, and cycle identifications are included.

5.3.10 Verify that all signature/date entries are completed. Performed By and Verified By signatures for critical operations must have the same date.

5.3.11 Verify that the procedure was followed. If steps were not performed or procedures were not followed as written, a deviation must be prepared and approved according to SOP 21301 - Deviations from Written Documents.

5.3.11.1 Insignificant deviations (Class 1 deviations) may be corrected and/or explained in the BPR.

5.3.12 Verify that filter integrity testing was performed (if required) and passes the acceptance criteria. Include documentation of filter integrity testing in the BPR (if applicable).

5.3.13 Verify that calculations are correct and accurate.

5.3.14 Verify that measurement units are recorded as required (for example: g, µg, ºC, AM, PM, military time, etc.).

5.3.15 Verify that in-process environmental monitoring was performed (if required) and that results have been evaluated / reviewed by BQA.

5.3.16 Verify that in-process inspection results are included (if required) and that all issues were addressed.

5.3.17 Verify that in-process PA\QC testing was submitted by checking that a copy of the PA\QC Test Request, Form 22002-01, is in the batch record. Where required in the BPR, verify that PA\QC test results are included in the record.

5.3.18 Verify that the label approval and reconciliation was completed according to SOP 21403 - Origination, Modification, and Control of Labels for GMP and GLP Products, if applicable.

5.3.19 Verify that time restrictions are correct, accurate, and followed.

5.3.20 Verify that final product inspection was performed according to SOP 15113 - Inspection of Unlabeled Vials of Finished Product, and SOP 15125 - Inspection of Labeled Vials of Finished Product, if applicable.

5.3.21 Verify that the product was stored under appropriate conditions throughout the procedure as specified in the BPR.

5.3.22 Verify that the batch record was completed following appropriate documentation practices outlined in SOP 21409 - Good Documentation Practices.

5.3.23 Verify that the buffers used for the production have been reviewed and released as per SOP 15100 - Preparing Reagent Solutions.

5.3.24 Verify that the complete batch product record has been signed by the Project/ Production Supervisor or authorized designee.

5.4 BQA will record any deficiencies during the review of the BPR and make recommendations (if appropriate) for corrective action on Production Record Review Findings, Form 21103-02. Listed findings must include a reference to the page number and/or section of the BPR where the deficiency is located, when possible.

5.5 When the initial BQA review is completed, the batch record is, if necessary, returned to the Project/Production Supervisor or designee with the BQA Batch Production Record GMP Review Findings (Form 21103-02). A written reply to the findings and/or appropriate corrections to the BPR will be completed by the Supervisor or designee and the batch production record is returned to BQA for verification.

5.6 When the issues/deficiencies have been satisfactorily addressed, BQA shall complete the "Resolved" section of Forms 21103-01 and 21103-02 for the reviewed BPR.

5.7 The BPR, when completed, is processed as in step 9.0 below.

6. REVIEWING COMPLETED BATCH PRODUCTION RECORDS/LAB NOTEBOOKS FOR GLP PRODUCTION

6.1 Upon completion of a BPR or a lab notebook documented project, the BDP Project/ Manufacturing Supervisor reviews the document for technical accuracy and completion and submits the document to BQA.

6.2 Receipt of the completed BPR or lab notebook is entered in the tracking database.

6.3 BQA reviews the batch production record or lab notebook using the following guidelines and records the results on Form 21103-02, Production Record Review Findings.

Batch Record Review Guidance

6.3.1 Verify that the completed batch production record is an accurate reproduction of the master if issued by QA.

NOTE: A draft BPR may be used. Verify that all pages are included and that the most recent revision was issued as appropriate for an issued BPR.

6.3.2 Verify that the lot number recorded is accurate by checking the lot number logbook maintained by BQA.

6.3.3 Verify that the BPR contains a list of all employees who performed the process, including unique signature and initials for each.

6.3.4 Verify that entries are complete and that raw materials were used prior to expiration (where expiry is assigned).

6.3.5 Verify that equipment used was within the calibration or certification expiration date.

6.3.6 Verify that weigh records are complete, properly labeled, and reflect the correct quantities needed per formulation requirements and are initialed and dated.

6.3.7 Verify that signature/date entries are completed.

6.3.8 Verify that the procedure was followed. If steps were not performed or procedures were not followed as written, assure that the process that was performed has been adequately documented.

6.3.9 Verify that calculations are correct and accurate and include units of measure (for example: g, ug, oC, AM, PM, military time, etc.).

6.3.10 Verify that in-process inspection results are included (if required).

6.3.11 Verify that any required in-process PA\QC testing was submitted by checking that a copy of the PA\QC Test Request, Form 22002-01, is in the batch record.

6.3.12 Verify that the label approval and reconciliation was completed according to SOP 21403 - Origination, Modification, and Control of Labels of GMP and GLP Products, if applicable.

6.3.13 Verify that processing times are documented, when necessary.

6.3.14 Verify that the buffers used for the production have been reviewed and released as per SOP 15100 - Preparing Reagent Solutions.

6.3.15 Verify the record has been reviewed by the Manufacturing Supervisor or authorized designee.

Lab Notebook Review Guidance:

6.3.16 Verify that the lot number recorded is accurate by checking the lot number logbook maintained by BQA.

6.3.17 Verify that the lab notebook identifies the equipment and material used and the personnel involved.

6.3.18 Verify that raw materials are properly identified and were used prior to expiration (where expiry is assigned) and that the entries are complete.

6.3.19 Verify that equipment used was within the calibration or certification expiration date, if applicable.

6.3.20 Verify that signature/date entries are completed.

6.3.21 Verify that calculations are correct and accurate and include units of measure (for example: g, µg, °C, AM, PM, military time, etc.).

6.3.22 Verify that processing times are documented if required.

6.3.23 Verify the record has been reviewed by the Manufacturing Supervisor or authorized designee.

6.3.24 Verify that a sample or copy of the final product label is present and that labeling has been reconciled. Verify that the label (if present) has a lot number, manufacturing date and a caution statement appropriate for the intended use of the material (Not For Use In Humans or R&D Use Only), as applicable.

6.4 BQA will record any deficiencies during the review of the BPR or lab notebook and may make recommendations for corrective action on Form 21103-02. Listed findings must include a reference to the page number and section of the BPR or lab notebook where the deficiency is located.

6.5 When the initial BQA review is completed, the batch record or lab notebook is returned, if necessary, to the Project/Manufacturing Supervisor or designee through BQA with the BQA Production Record Review Findings (Form 21103-02). A written reply indicating that the appropriate corrections to the BPR or lab notebook have been completed is required. The batch production record or lab notebook is returned to BQA for verification.

6.6 When the issues/deficiencies have been satisfactorily addressed, BQA completes the "Resolved" section of **Forms 21103-01** and **21103-02**.

6.7 BQA shall signify review of the document by using the BQA “Reviewed by” stamp, with initials and date.

6.8 Submit the BPR or lab notebook including Forms 21103-01 and 21103-02 to the BQA Audit Manager or designee for a review/approval signature. The completed BPR is processed as in Step 10. below. Lab notebooks either may be returned to the owner of the lab notebook for continued use or, if completed, may be filed. If a lab notebook will be returned for continued use, then a true and exact copy shall be made of the appropriate pages and and the copied pages filed in the project file.

7. REVIEWING COMPLETED BATCH PRODUCTION RECORDS FOR NON-GMP/NON GLP PRODUCTION

NOTE: Non-GMP/Non-GLP productions include practice runs, pilot runs, research and development runs, and runs generating reference materials that result in material with an assigned lot number. The use of a draft unapproved MPR is allowed for non-GMP/non-GLP products.

7.1 Upon completion of the production record (BPR or lab notebook), the BDP Project/Manufacturing Supervisor, or designee, reviews the document for technical accuracy and completion, signs the document, and forwards the document to BQA.

7.2 Receipt of the completed record is entered by BQA in the tracking database and forwarded to the BQA Auditor assigned to the project.

7.3 BQA reviews the production record using the following guidelines and records the results on Form 21103-02, Production Record Review Findings.

7.3.1 Verify that the lot number recorded is accurate by checking the lot number logbook maintained by BQA.

7.3.2 Verify that the BPR or lab notebook contains the purpose, methods, identifies the equipment and material used, and includes data, results, and conclusions, as appropriate.

7.3.3 Verify that the label, (if present) has a lot number, manufacturing date and a caution statement appropriate for the intended use of the material (Not For Use In Humans or R&D Use Only), as applicable.

7.3.4 If the material was made in a CGMP area, verify that the listed equipment used and the production areas have been cleaned, postproduction campaign cleaning, and the cleaning documented using the approved records/forms for the equipment and areas.

7.4 BQA will document any significant deficiencies during the review of the documentation and make any recommendations for corrective action on Form 21103-02. Listed findings must include a reference to the page number and section of the production record where the deficiency is located, when possible.

7.5 When the initial BQA review is completed and significant deficiencies were noted, the production record is returned to the Project/Manufacturing Supervisor or designee through BQA with the BQA Production Record Review Findings (Form 21103-02). A written reply or appropriate corrections to the production record should be completed and the record returned to BQA for verification.

7.6 When the issues have been satisfactorily addressed, BQA shall complete the "Resolved" section of Form 21103-02 for the BPR reviewed.

7.7 BQA shall signify review of the document by using the BQA “Reviewed by” stamp, with initials and date.

7.8 The completed record is process per Step 9.0 below.

8. DOCUMENTATION OF THE REVIEW

8.1 Document the record review on the appropriate record review checklist (Form 21103-01). The "Issue Resolved" column must indicate that any unsatisfactory issue has been resolved. A reference to Form 21103-02 is acceptable to show that the issue has been resolved.

8.2 Document issues requiring corrective action on the Production Record Review Findings (Form 21103-02). Use the “Finding” column to record deficiencies or explain why any result is not satisfactory. Use the “corrective action” column to recommend (as appropriate) how to correct the noted deficiency.

8.3 Upon completion of the Production Record Review Checklist the Production Record Review Findings Form, submit these documents along with the BPR/lab notebooks to BQA for filing in the Controlled Documents Room.

8.4 Responses to BPR findings by BDP personnel may be documented on Form 21103-02 or on a separate page if more space is needed for comments.

9. STORAGE OF COMPLETED BATCH RECORDS AND OTHER PRODUCTION RECORDS.

9.1 BQA archives completed, as well as other production records, as submitted by Manufacturing.

9.1.1 Completed batch records that have been reviewed and signed by BQA are stored in blue folders in numerical order by project and lot number.

9.1.2 Lab notebooks may be either returned to the owner of the lab notebook for continued use or, if completed, forwarded to BQA for filing. If a lab notebook will be returned for continued use, then a true and exact copy shall be made of the appropriate pages and filed in the project file.

9.1.3 Batch records are stored by BQA as per SOP 21402 - Archived Documents.

10. REFERENCES AND RELATED DOCUMENTS

Document Number	Title
15100	Preparing Reagent Solutions
15113	Inspection of Unlabeled Vials of Finished Product
15125	Inspection of Labeled Vials of Finished Product
21301	Deviations from Written Documents
21402	Archived Documents
21403	Origination, Modification, and Control of Labels for GMP and GLP Products
21409	Good Documentation Practices
21415	Preparation, Issue, Completion, and Approval of Master Product Records
21103-01	Batch Production Record Review Checklist
21103-02	Production Record Review Findings