The review of batch production records coupled with the trending of yields and deviations are key parts of the quality assurance process for the manufacturing of drug products. Batch record review is typically a verification step that confirms the acceptability of the manufacturing and packaging processes. If, however, a pattern of corrections or deviations emerges, a firm gains valuable information from investigation that can lead to both corrective and preventive action—even process improvement. Process drift can be detected before yield or other parameters exceed alert or action limits. Because the review process is so common, its importance may be overlooked beyond the regulatory requirement found in the current good manufacturing practices regulation. Proper controls and corrective action can prevent well-intentioned manufacturing steps from creating products that are adulterated. Useful suggestions are offered and several scenarios illustrate what can happen when the review process is not standardized and monitored.

INTRODUCTION

This article provides background on the importance of the records that support manufacturing of finished drug products. It focuses on the batch record review process and its importance as a vital step in the quest for quality in manufactured drug products. For those new to this industry, a bit of background may be useful to put the importance of the review of batch production records (BPRs) and other production and control records into practical and regulatory perspective before discussing the various facets of the review process. While this article is aimed at BPRs for drug products and the active pharmaceutical ingredients (APIs) used to manufacture drug products, many of the concepts presented herein are also applicable to the review of other types of manufacturing records.

Regulatory Basis

Before discussing the various records required for the manufacture of finished drug products as identified in the current good manufacturing practices (CGMPs) regulation as published by the US Food and Drug Administration, it is useful to cite a key section of the Federal Food, Drug, and Cosmetic Act (1). The act states the following:

A drug or device shall be deemed to be adulterated …if it [the product] is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

This excerpt should remove any misunderstanding about the need for appropriate controls. In fact, in most cases when a compliance officer for FDA District Office sends a warning letter to a firm for identified deficiencies, the cause is typically for lack of controls or inadequate records and reports to support proper manufacture. It most often is not for a contaminated product as the term “adulterated product” is frequently misinterpreted. Both from a regulatory requirement and a practical management of the processes perspective, records and reports corroborate that appropriate controls
were in place and were followed when a subject product was manufactured.

**CGMP Requirements**

Key requirements for production and control records are found in Subpart J of 21 CFR Part 211, which is one of the larger sections of the FDA CGMP regulation (2). This section contains the following specific sections:

- §211.180. General requirements
- §211.182. Equipment cleaning and use log
- §211.184. Component, drug product container, closure, and labeling records
- §211.186. Master production and control records
- §211.188. Batch production and control records
- §211.192. Production record review
- §211.194. Laboratory records
- §211.196. Distribution records
- §211.198. Complaint files.

Each of the listed records or group of records fulfills a portion of the overall quality assurance goal. These records, in total, identify approved materials, the status of each component, the cleaning status, and previous use of each piece of equipment. Those who manufacture and package drug products are guided in the execution of each manufacturing step and the recording of data; likewise for those who package and label product. Results from samples taken at various points in the process confirm that the finished product contains the correct active ingredient or ingredients in the proper amounts. When environmental monitoring is required, data are recorded to verify that the manufacturing area or suite is suitable. Balances and scales require metrology records for their testing and calibration. Further, records of verification of balances or scales with known weights before use are typical industry practice. Even more records may be required for some operations. One can quickly understand the responsibility for keeping records is an important one, and the list is extensive for manufacturing drug products.

One is well advised to understand the importance of these various records from a regulatory perspective based on the emphasis placed on them in the CGMP regulation. Note the length of the section and the level of detail provided. Batch production records capture the many activities that support compliant drug product manufacturing as well as the direct manufacturing, packaging, and labeling steps that may be reviewed. Records are the proof of what was done, when it was done, and who did it. Laboratory records then provide confirmation that active ingredients are detected in the correct amounts from samples taken from the production lot and that the dosage form will deliver the active ingredients as designed.

Production and control records are among the most reviewed records in any typical regulatory inspection or audit. This emphasis on the importance of production and control records should not be misconstrued as justification to omit any of the other required records. Each provides the detail required for a complete picture of the manufacturing process and testing process.

**MASTER PRODUCTION RECORD**

The master production record (MPR) (requirements found in 21CFR 211.186) identifies both the sequential steps for the manufacturing process along with any process parameters that must be met. These parameters, often expressed as an acceptable range, are the same as those confirmed during the validation of the process and, of necessity, are consistent with the regulatory filing that supports the manufacturing of the product. The MPR is usually the culmination of technology transfer, scale-up, successful validation batches, and verification that the manufacturing steps align with any regulatory filings. The Chemistry, Manufacturing, and Controls (CMC) section of a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) filed in the US represents a “promise to make the product in the stated manner.” The implications of any significant departure from this master production record should be self-evident.

**BATCH PRODUCTION RECORD**

Whether called batch record, batch production record (BPR), production control record, production record, production batch record, or some other term, this document refers to the step-wise procedure that operators or technicians follow to manufacture a drug product. Batch production and control records are described in §211.188, as follows: “Batch production and control re-
cords shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch” (2).

Each BPR is a controlled document from the time it is issued until it can eventually be destroyed. It contains the same information as found in the MPR because it is “an accurate reproduction of the appropriate master production or control record” that has been checked for accuracy, dated, and signed. The record will be executed by various operators to “document that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished” (2). These include, among other things, the following:

- Dates; many firms also require times
- Identity of individual major equipment and lines used
- Specific identification of each batch of component or in-process material used
- Weights and measures of components used in the course of processing
- In-process and laboratory control results
- Inspection of the packaging and labeling area before and after use
- A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing
- Complete labeling control records, including specimens or copies of all labeling used
- Description of drug product containers and closures
- Any sampling performed
- Identification of the persons performing and directly supervising or checking each significant step in the operation
- Any investigation made according to 211.192
- Results of examinations made in accordance with 211.134.

It is noteworthy to emphasize that “control” is at the heart of the current good manufacturing regulation and this control extends to every critical step in the manufacturing and packaging process. The BPR for each batch is an extension of this control because it is not sufficient to rely solely on laboratory results to release a product for sale. Laboratory data should confirm the expected results of the process. Each batch has been manufactured with process controls. The BPR provides a step-by-step documentation of these manufacturing controls. The completed BPR becomes the verification that all critical steps were performed as prescribed and, when combined with laboratory results, the manufacturing firm has adequate documentation for batch disposition. The practical need for good documentation parallels the requirements of the CGMP regulation.

BACKGROUND ON THE REVIEW PROCESS

Once the manufacturing or packaging has been completed and the record has been returned to those in the quality unit that log in such documents, the next task is to review the batch production record for accuracy and conformance to established documentation standards. The author recommends the review of a BPR or packaging record by manufacturing or packaging supervisory personnel before returning the record to the quality assurance (QA) department.

Just as manufacturing and packaging are subject to standard operating procedures (SOPs), so should the review process. The regulatory requirement for BPR review is found in 21CFR 211.192 and 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 products before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow up.”

Each batch record is typically specific to the product and product strength because of the quantities of the active pharmaceutical ingredients and excipients required. In the case of tablets, the batch record may in-
dicate by picture, line drawing, or description the size, shape, color, and any embossing on the tablet. If the tablet is film coated, the lettering on the tablet and its color may be shown. In the case of oral liquids, products can be described by color and any flavoring that may impart a characteristic odor to the product. These details will be found in the MPR.

Within the firm’s QA group responsible for reviewing BPRs, three documents are useful in guiding the review process: the BPR review SOP, a checklist to ensure completeness, and a summary of exceptions that may also be termed a “corrections sheet.” In some firms, the last two documents may be combined into a single document.

Just as the manufacture of products is guided by procedures and the BPR, the review of BPRs should also be the subject of an SOP. Even though the review of batch records may be less complicated than the manufacturing or packaging of drug products, an SOP should make the process more consistent and the checklist will ensure that critical steps and parameters are reviewed.

THE BPR REVIEW SOP

While this SOP does not need to be lengthy, it does need to emphasize the importance of an accurate and thorough review of each BPR. Examples, which are provided within the SOP, help reviewers understand the scope and boundaries of their responsibility. The SOP should identify the key steps of the review process. These will include, but are not limited to, the following:

- Verifying that all pages of the BPR and any required supplemental pages or attachments are present
- Verification of the chronology of events, processing and hold times, are evident and within prescribed ranges
- Critical process parameters, specific to each subject product, should be reviewed to ensure that time, temperature, pressure, etc. are within specification
- Yield at each step in the process has been accurately calculated and is within specification (3)
- Good documentation practices (GDPs) have been followed by those who made entries and corrections to the BPR or any attachment.

The SOP typically sets a timeline for the completion of BPRs including any need for corrections. Some firms allow 30 days from the time the record is received in QA. Possible exceptions may be allowed if a deviation is cited and must be investigated. Here, too, a reasonable limit for investigations will ensure that they are closed in a timely manner.

The BPR review should be more than a robotic handling of paper or a purely mechanical process of looking for missing or incorrect information. Importantly, does the BPR tell a complete and correct story for the steps or processes involved in the BPR?

The BPR review SOP may specifically refer to a separate policy, standard, or another internal SOP that defines good documentation practice (GDP) requirements for the firm. These basic requirements typically include, but may not be limited to, the following:

- Entries must be legible.
- Entries must be in ink (typically ballpoint and, unless otherwise specified, dark blue or black ink are good choices).
- Entries must be dated (by page or by entry).
- Time entries should be consistent with internal standards (e.g., AM/PM time or 24-hour time).
- Entries are typically initialed by the operator or operators who performed (or observed) the step. A log of names and initials will be a valuable resource for reviewers, but a better option is to have each person who performs any step on a subject batch sign the BPR on a signature page.
- Calculations, weighing of materials, and addition of materials to the process must be verified. The initials and date—and usually time—of the person who performs the step and the initials and date of the person who observes the step are entered onto the BPR. If data are recorded automatically, a single signature may suffice.
- Corrections, if any, must bear initials and date of correction. An explanation of the correction is required by many firms and is a recommended step.
- Cited attachments are present and legible.

This SOP should provide details on when and how a reviewer should inform those who are responsible for initiating and investigating deviations if vital informa-
tion is missing or if a parameter, including yield, is out of specification.

THE BPR REVIEW CHECKLIST

The BPR review checklist highlights the key points that the BPR review should cover and typically requires the reviewer to initial each section that has been reviewed. These signoffs are particularly useful if the review process is interrupted by a need to obtain clarification or correction or if a second reviewer is required to complete a particular BPR review.

A specific checklist should be prepared for each type of finished drug product because the manufacture of tablets, capsules, and oral liquids vary by process and parameters. Products for parenteral administration typically require extensive environmental testing and microbiological testing to confirm sterility.

Such a checklist, even a specific one, supplements the SOP. It is not a replacement for an SOP. For illustration, the following steps may be found in a generic checklist or review summary that some firms use to document the review of each batch record. These steps are both generic and very basic; such steps should be adapted to meet the needs of a particular firm and its products. Some firms create checklists that are specific to a BPR or process. While this adds the responsibility of creating and maintaining additional checklists, the review is enabled by a checklist that identifies critical steps and/or other relevant parameters for the operation under review. The following are steps typically found in review checklists:

• Enter the name of the product, the product strength (packaging size if applicable), and the batch number on the checklist or review summary.
• Perform a page count and verify that the pages that are an integral part of the record are present and in order. Typically, BPR pages are numbered “Page x of xx.” Look also, during the review, for any additional pages such as copies of logs or added pages based on cited needs. While the bare BPR will be a copy of the MPR, the BPR and its supplemental pages will likely exceed those of the MPR.
• Verify that an authorized person properly issued the BPR and that it bears a signature and date of issue. Each firm must determine if the checklist for BPR review, which should be a controlled document, must be issued by an authorized person in the quality unit or if it may be printed as needed from an electronic folder whose access is controlled by password or other computer permission.
• Relying on established documentation standards, verify that all entries and corrections conform to internal expectations. These basic requirements were cited earlier.
• A bill of materials (BOM) will indicate what components and what quantities are expected for a particular batch against which the reviewer will compare entries in the BPR.
• The yield of product in terms of dosage units or in total mass should match the expected yield within specified limits. These limits are typically absolute and a reviewer should be instructed to cite any values that fall outside the specified range. See 21CFR 211.188(b).
• The BPR should be signed by an authorized person, typically one who is responsible for the manufacturing step. The reviewer should be able to determine from internal documents those who are authorized to sign BPRs.
• If any in-process generated charts or data are to be included as part of the BPR, verify their existence (examples include but are not limited to room environment charts, compression data such as compression force and rpm, temperature reading from solutions, cleaning records, maintenance records).
• If any exception is noted in the review of the BPR, initiate steps for correction or, if it warrants, verify that an appropriate investigation has been initiated.
• If the BPR is for packaging, verify that a sample label matches the image of the expected label. Label reconciliation must be performed or confirmed. Counts of labels are more accurate than weighing of labels and converting them to an approximate number.
• If applicable, the reviewer should indicate on a separate sheet or by electronic entry that exceptions have been noted and clarification is being sought within a firm’s devia-
tion reporting and investigation process.
• The BPR checklist or review summary should be signed and dated when completed and then returned with the BPR to the appropriate secure area once the results of the review have been communicated to the appropriate personnel, which is frequently accomplished by updating the status of a BPR in an electronic tracking system.

CORRECTIONS TO THE BATCH RECORD
The ultimate goal of batch record review is not merely to identify exceptions (e.g., mistakes, oversights, illegible entries, etc.), but to have the record corrected in a timely manner so that it provides accurate documentation of the steps that comprise the manufacturing or packaging of the cited batch. Batch records may be reviewed for information again in weeks, months, or years after a subject batch has been manufactured or packaged or may be identified for review as part of a regulatory inspection. They need to be corrected before being stored.

Although the importance of BPRs is undisputed, there are logistical challenges in the correction process. These arise from the need to control the BPR and the availability of the required personnel to make corrections. Ideally, all entry mistakes should be identified in the departmental review before the record is returned to QA for the quality review. If such a review is conducted, the instructions must be clear that the review is to identify any missing information and that entries are correct and within established parameters. The author has observed that this review can deteriorate to nothing more than a check for blank spaces in the records—a process of limited value.

Assuming, however, there is a question or required correction at the QA review level, the person who made the original entry (or failed to make the entry) on the BPR meets with the reviewer who identified the exception. This question or required correction will be noted on the “corrections sheet” in sufficient detail to allow any subsequent person to understand the concern. After discussion, if needed for clarification, the BPR correction or corrections are made by the operations person and verified by the reviewer. This assumes a departmental supervisory signature or initials are not required. When an immediate correction is not possible due to shifts, person on vacation, etc., then the reviewer must inform the person who needs to review the BPR to identify a time this may be done. Corrections to records compete for the time of operating personnel so it is helpful to be very specific on what the question or needed correction is. Partially completed BPRs pose a logistical and document control challenge. A procedure is needed to describe how and where such records are to be stored and who is responsible for completion if the reviewer who started the review is not available for completion in a timely manner.

There are occasions when vital information is missing and cannot be corroborated through electronic or other records. The reviewer then has the responsibility to inform those who are responsible for internal deviations and investigations. This step should be noted on the BPR so that record is complete with a link to the investigation. Completion of the BPR review will be delayed until the investigation has been completed and the disposition of the deviation is determined. The review should be completed and signed even if the batch is to be reworked—if allowed—or destroyed. The BPR and the checklist and corrections sheet should then be returned to the QA storage area and the review status updated in the BPR status log or database.

PERIODIC REVIEW OF THE BPR REVIEWS
The author suggests periodic supervisory or managerial reviews within the quality unit to determine that the desired consistency is being achieved. A review of corrections sheets from various reviewers will provide useful insight into the number of exceptions cited and/or required corrections, the types of exceptions noted or corrections sought, and a comparison of the findings by the various reviewers. Just as trending production results is a useful tool to detect any drift in the manufacturing process, it is useful to examine the reviews of BPRs to detect drift or other trends that may identify corrective steps that should be taken. If the number of corrections is high, then one must question if manufacturing personnel and BPR reviewers have the same understanding of what constitutes accurate and sufficiently complete BPR documentation. If a misunderstanding exists, perhaps the initial training for manufacturing personnel, quality personnel, or both was not sufficiently detailed.
Or, is the language in the BPR ambiguous and thus misinterpreted? The goal is to ensure that manufacturing personnel and reviewers are working toward the same goal of good documentation.

From a slightly different perspective, if the type of exceptions or required corrections is high for a particular BPR, then the language of that BPR should be carefully examined. If the language appears to be clear, then the documentation sought should be reviewed with affected manufacturing personnel. Is the variation noted primarily on one shift? Is additional training required? If the language is ambiguous, perhaps the next step is to follow the firm’s change control procedure to modify the SOP followed by retraining.

Finally, is there a discrepancy among individual reviewers on the number and types of exceptions noted or corrections sought? This determination can lead to useful discussion and “fine tuning” to make the review process more consistent among all reviewers.

Inconsistency in the review process may include the scenarios provided, but this is not complete. Each type of inconsistency can be detected through periodic assessment and corrected by supervisory intervention.

Inconsistency Scenario 1: Expediency Versus Accuracy
As anyone who has spent time reviewing BPRs can tell you, the task is tedious, repetitive, and demanding. Because the steps required to obtain corrections to documents requires additional time and follow-up, a reviewer may fall into the habit of minimizing the number of corrections required on a document as a way to close them faster. This is a dangerous trend because shortcuts tend to become habits, and the inconsistency introduced by not reviewing all prescribed parts of a BPR or related record can leave gaps that should have been addressed. Useful feedback to manufacturing may be missed when such shortcuts are routinely taken. When “just getting through the record” becomes the goal instead of ensuring that the record provides correct and reliable information about the process, two results are likely. First, the accuracy of the record and the information it provides becomes suspect. Second, manufacturing personnel are deprived of the opportunity to learn of mistakes or misunderstanding that could lead to improvement.

Inconsistency Scenario 2: Drift (Unintentional)
Closely associated with the first scenario is a phenomenon we’ll call drift. This scenario may be likened to instruments that are periodically calibrated to ensure that the accuracy of their measurements is reliable. In this scenario, a well-trained and experienced reviewer has reviewed so many records that they have unintentionally “drifted” from the internal standard. While this reviewer has access to the relevant SOP and checklist for record review, those guiding documents are no longer needed, even though the checklist may be signed. The review process has taken on a somewhat robotic activity during which the mental process is not fully engaged. This drift can introduce inconsistency by unfortunately missing critical gaps in data or incorrect entries. Discovery of such drift in the review process can be unnerving to those in quality management because it is difficult to determine how many record reviews are suspect and potentially unreliable. This inconsistency may surface when periodic audits of the reviews conducted by various reviewers show very different findings. The feedback to manufacturing can be confusing because there is a lack of consistency in the way particular parts of records are routinely completed.

Inconsistency Scenario 3: Overkill
While the lack of full attention to the review process is one source of consistency, so is the reviewer who goes far beyond the internal standard. In this scenario, the reviewer insists that every detail, however inconsequential, be corrected to her/his standard. This may even include challenging the grammar and spelling of those who have otherwise written a satisfactory comment or correction in the record. One will hear justification for this overly zealous approach in statements such as, “If you want me to sign this record, then it must be absolutely correct,” or, “I’m just not comfortable with this record.” Not only does this overkill in the review process consume additional effort on the part of manufacturing personnel to make the corrections, it sends an unfortunate message to those who make the product. The acceptability of a record seemingly depends more on who reviews the BPR than on how the record was completed. Any inconsistency in the BPR review process challenges the reputation of the quality unit and its management
because it demonstrates a lack of appropriate oversight of its staff. Oversight is one of the key roles of the quality unit in most organizations. Quality unit management must ensure that its personnel also consistently meet established standards.

SUMMARY
The types of controls and the records and reports that support them for the manufacture of finished drug products are well defined both in terms of regulatory requirements and in industry practice. Adequate review of executed BPRs serves at least two important purposes. The process satisfies the regulatory requirement for such a step, and the process provides useful feedback to the functional group responsible for the manufacturing step. As noted, a high error rate may indicate improper training or inadequate supervision, but it may also indicate a poorly written procedure. Properly trained reviewers and approvers of BPRs provide a valuable service to the quality assurance unit of a manufacturing organization. Their training should include a goal of consistency in the review process in addition to accuracy and thoroughness; this can best be determined by periodic supervisory review of the findings of reviewers.

REFERENCES

ABOUT THE AUTHOR
David Jones is an independent consultant who works with pharmaceutical clients to improve their document control and their documentation practices. He has guided teams for the review of batch production records and has learned by experience the challenges of the BPR review process. Having learned how to make the review process both effective and efficient, he shares these tips with clients and readers. David also assists clients by guiding the improvement of production records to make them more operator-friendly, thus reducing errors and deviations, and wherever possible, reducing the size of such records. David can be reached via e-mail cgmpman@aol.com or by telephone at 804.350.5410.