Regulations

• Regulations specify what must be included in a batch record…
• And…
• What must be reviewed for batch release.
A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions, and should contain the following information:

a) The name and batch number of the product;
b) Dates and times of commencement, of significant intermediate stages and of completion of production;
c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
d) The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
e) Any relevant processing operation or event and major equipment used;
f) A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
g) The product yield obtained at different and pertinent stages of manufacture;
h) Notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;
i) Approval by the person responsible for the processing operations.

Note: Where a validated process is continuously monitored and controlled, then automatically generated reports may be limited to compliance summaries and exception/out-of-specification (OOS) data reports.
EU QA Review Requirements

EU GMP 6.3 [Quality] Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.
§ 211.186 Master production and control records.

(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.
(b) Master production and control records shall include:
(1) The name and strength of the product and a description of the dosage form;
(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;
(3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;
(4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;
(5) A statement concerning any calculated excess of component;
(6) A statement of theoretical weight or measure at appropriate phases of processing;
(7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to §211.192 is required;
(8) A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;
(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.
21CFR211

• § 211.188 Batch production and control records.
• Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:
• (a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed;
• (b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:
  • (1) Dates;
  • (2) Identity of individual major equipment and lines used;
  • (3) Specific identification of each batch of component or in-process material used;
  • (4) Weights and measures of components used in the course of processing;
  • (5) In-process and laboratory control results;
  • (6) Inspection of the packaging and labeling area before and after use;
  • (7) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;
  • (8) Complete labeling control records, including specimens or copies of all labeling used;
  • (9) Description of drug product containers and closures;
  • (10) Any sampling performed;
  • (11) Identification of the persons performing and directly supervising or checking each significant step in the operation;
  • (12) Any investigation made according to § 211.192.
  • (13) Results of examinations made in accordance with § 211.134.
§ 211.192 Production record review.

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. 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 followup.
Summary of GMP Requirements for Batch Review/Release

Batch Review:
A member of quality must review the Batch Production Record to ensure that the batch has been executed on conformance with approved procedures.

Batch Release:
Batch Related Quality and production records have been completed and reviewed by authorized production and quality unit personnel.
Traditional Batch Record Review:

• QA Reviews ALL execution of paper batch production records.
  • Deviations were identified and investigated.
  • Documentation errors were identified and corrected.
• All associated paperwork was reviewed
  • Sterilization records
  • Cleaning records
  • Equipment setup/check records
  • Raw material/Excipient records
Problems?

- Traditional process was costly and time-consuming
- This process did not leverage risk based thinking....
A New Way of Thinking…

- PIC/S QBD Q8/9/10
- GMPs for the 21st century (FDA)
- PAT initiative (FDA)
- New guidance on PV from EU and FDA

- Part 11 Guidance and Revised Annex 11
- MHRA Data Integrity Guidance
Batch Review by Exception

• In the context of batch review, when batch execution is documented in a well-designed manufacturing execution system (MES) that enforces various controls over that execution to ensure batches are produced meeting all required elements of their respective control strategies thus ensuring all critical quality attributes are acceptable, the review of the completed batch processing records need only be the exceptions to the normal process. This is possible because batch parameters and manufacturing instructions are, under normal operation, controlled and ensured compliant by validated IT or automated systems. The “review by exception” then occurs only in those situations when additional actions are required (i.e. response to alarms, log entries, non-confirmed cycle completions, and atypical events that occasionally occur).
Strategy

- Create a list or map of all control points of process. This should include all aspects of manufacturing. Such as process parameters critical to product quality or raw material/excipient identification and quantity.
- Design automated checks for all these items in MES, automation systems, or LIMS.
- Decide whether users need the ability to change configuration or override this automated functionality.
  - If they CANNOT, much less to review. We can allow systems to ENFORCE certain controls.
  - If they CAN, more to review, changes will need to be identified and reported. These EXCEPTIONS would then need to be reviewed.
In his presentation, Dr. Watts explained that Process Analytical Technology was to be used for; manufacturing analysis and control, measuring, processing, materials, and processes.

He also said that the term “analytical” was to be used broadly and include not only chemical and physical measurements but also mathematical and risk analyses all to be used in an “integrated manner.”
Dr. Watts emphasized that a PAT approach should focus on “process understanding” and Quality by Design. He explained that experimental design should determine which parameters are critical to product quality. Then he asks how a manufacturer could analyze and control these parameters.
Production Record Design

- Production Record Sequence managed in MES.
  - Cannot manufacture out of sequence
  - Solution manufacturing charging of excipients and QS enforced
  - Validated time limits are enforced
  - All equipment cleanliness/sterilization checks are performed automatically and enforced
  - RABS and/or Isolator glove integrity testing enforced
  - Isolator sterilization cycles enforced
  - Room sanitizations enforced
  - Material usages checked
  - All equipment cleaning is now traceable to batch
MES Ticket Design

• Required checks that the equipment and area are clear of previous products, documents, or materials not required for the planned process

• Proper setup of equipment is enforced
  • Tanks
  • Washer
  • Depyrogenation Tunnel
  • Filling equipment
  • UAF hoods
  • Transfer station/filling lines

• Execution of each ticket enforces key steps/processes such as mixing/recirculation or sampling
Process Automation Controls

- Automation layer enforces recipe requirements for process.
  - Manufacturing operation is controlled.
  - Automatic discarding when a condition is not met.
  - Rejection of non-conforming product (PAT)
  - Logging interventions into aseptic environment.
  - Automatically generating in-process control samples.
Recipe/Parameter Design

- Recipe/Parameter management at HMI level.
  - Recipes are approved electronically, MES enforces only correct recipe is used. HMI layer assures only current approved version is loaded.
  - Only certain parameters are modifiable at HMI and appear on batch report.
Design for Exceptions

• Typical MES Exception Practices:
  • Logs generated with quality related exceptions (such as certain quality critical alarms or execution issues arise).
  • Mandated QA reviews when exceptions require specific QA signoff (such as sterilizations).
  • All MES batch records have enforced open log reviews before they can close.
Batch Production Record Exceptions Requiring Quality Review -
An example of how to meet GMP expectations…

MES production tickets will ensure that processing is carried out in accordance with the instructions contained in the batch production records. Where exceptions can occur, they are identified for batch review as follows:
## MES Exceptions:

<table>
<thead>
<tr>
<th>Production Record Requirements</th>
<th>MES</th>
<th>Exceptions</th>
<th>Batch Review needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval to forward process</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Production records clearly state when approval is required for forward processing of material, and identify the approval authority required. System controls are applied to prevent the inadvertent continuation of processing when predetermined criteria (e.g., second person verification, analytical test requirements) are not met.</td>
<td>MES enforces this requirement</td>
<td>log creation</td>
<td>logs</td>
</tr>
<tr>
<td>Parameters critical to the process (FDA PAT guidance)</td>
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<td></td>
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</tr>
<tr>
<td>MES Production ticket versions clearly indicate the process parameters critical to the process and the corresponding acceptance limits.</td>
<td>The limits are Included in MES.</td>
<td>Critical alarms are generated in process automation system when outside of limits.</td>
<td>All critical alarms are on batch review report</td>
</tr>
<tr>
<td>Data entry</td>
<td></td>
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</tr>
<tr>
<td>MES Production ticket versions provide sufficient spaces for entry of data and signatures, including second person verification, where required. System controls are applied to prevent the inadvertent continuation of processing when entry of data and signatures are not met.</td>
<td>Included in MES</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Production Record Requirements</td>
<td>MES</td>
<td>Exceptions</td>
<td>Batch Review needed</td>
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</tr>
<tr>
<td><strong>Product information</strong></td>
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<tr>
<td>MES Production ticket versions contain the following product information:</td>
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<td></td>
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<tr>
<td>a. product name,</td>
<td>Included in MES</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>b. item code,</td>
<td>Included in MES</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>c. description of the product (for final drug product, the description must include the pharmaceutical dosage form, strength, and pack size expressed in terms of the weight or volume of the product in the final container),</td>
<td>Included in MES</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>d. space to enter the assigned batch or control number,</td>
<td>Included in MES</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>e. batch size, and</td>
<td>Included in MES</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>f. country or zone of destination, where applicable (e.g., packaging records).</td>
<td>Included batch records</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Equipment and location</strong></td>
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<tr>
<td>MES Production ticket versions contain the following details related to equipment and the production location.</td>
<td></td>
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</tr>
<tr>
<td>a. production location and major equipment to be used,</td>
<td>Included in MES</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>b. required checks that the equipment and area are clear of previous products, documents, or materials not required for the planned process,</td>
<td>MES enforces this requirement</td>
<td>Automatic log creation</td>
<td>Mandatory log review</td>
</tr>
<tr>
<td>c. required checks that equipment is clean and suitable for use,</td>
<td>MES enforces this requirement</td>
<td>Automatic log creation</td>
<td>Mandatory log review</td>
</tr>
<tr>
<td>d. methods to be used for preparing critical equipment (e.g., cleaning, assembly, calibrating, sterilizing), and</td>
<td>MES enforces this requirement</td>
<td>Automatic log creation</td>
<td>Mandatory log review</td>
</tr>
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<td>Production Record Requirements</td>
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<td>Exceptions</td>
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<tr>
<td>Material and component usage</td>
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<tr>
<td>MES Production ticket versions contain details regarding material and component usage including the following:</td>
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</tr>
<tr>
<td>a. a list of all materials and components to be used and described using a name or reference which is unique to that material,</td>
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<tr>
<td>b. an accurate statement of weight or measure of each material and component used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production is included. Reasonable variations may be permitted provided they are justified, and</td>
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<td>c. statement of any calculated excess of materials and components.</td>
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<tr>
<td>MES enforces this requirement</td>
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<td>Mandatory log review</td>
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<tr>
<td>Yield</td>
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<td>MES Production ticket versions include:</td>
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<tr>
<td>a. the theoretical weight or measure at appropriate phases of processing, and</td>
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<tr>
<td>b. the expected yield, including maximum and minimum limits beyond which a deviation is required.</td>
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<td>c. the actual yield and the percentage of theoretical yield obtained, at appropriate phases, must be included in the batch production record.</td>
<td></td>
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<td>MES enforces this requirement</td>
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<td>b. an accurate statement of weight or measure of each material and component used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production is included. Reasonable variations may be permitted provided they are justified, and</td>
<td></td>
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<td>c. statement of any calculated excess of materials and components.</td>
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<td>a. the theoretical weight or measure at appropriate phases of processing, and</td>
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<tr>
<td><strong>Processing instructions</strong></td>
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<td></td>
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</tr>
<tr>
<td>MES Production ticket versions include detailed step-by-step processing instructions (including directions to other control documents or systems) as follows:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. sequences to be followed,</td>
<td>MES enforces this requirement</td>
<td>Automatic log creation</td>
<td>Mandatory log review</td>
</tr>
<tr>
<td>b. all process parameters that directly impact critical quality attributes (e.g., critical limits) and their acceptable ranges,</td>
<td>The limits are Included in MES.</td>
<td>Critical alarms are generated in process automation system when outside of limits.</td>
<td>All quality critical alarms are on batch report</td>
</tr>
<tr>
<td>c. time limits for completion of individual processing steps and the total process, where appropriate,</td>
<td>MES enforces this requirement</td>
<td>Automatic log creation</td>
<td>Mandatory log review</td>
</tr>
<tr>
<td>d. sampling instructions and testing requirements,</td>
<td>MES enforces sampling requirements/ Darwin enforces testing requirements</td>
<td>Automatic log creation in MES for sampling/testing in LIMS</td>
<td>Mandatory log review in MES/testing in LIMS</td>
</tr>
<tr>
<td>e. instructions for in-process controls and any employed process analytical technologies together with their corresponding acceptance criteria</td>
<td>MES enforces this requirement along with IPC book functionality</td>
<td>Automatic log creation</td>
<td>Mandatory log review</td>
</tr>
<tr>
<td>f. where appropriate, special notations and precautions to follow or cross references to these (e.g., safety cautions for material and equipment handling).</td>
<td>Included in MES</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Storage requirements</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MES contains storage requirements, where necessary, including container, labeling, and special storage instructions with time limits.</td>
<td>Included in MES</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Non-Integrated Exceptions

- Reporting from these systems must be defined.
- Examples might include:
  - Filter integrity testing
  - Water and Air
  - HVAC
  - Maintenance of equipment (calibrations)
  - Cleaning of equipment or facility
  - Environmental monitoring
Batch Reporting

- Will include all the exceptions for each batch and summary of batch manufacturing
- Intent is “paperless” process with few exceptions:
  - Required process checks
  - Filter integrity testing
  - Water and Air
  - HVAC
  - Maintenance of equipment (calibrations or equipment checks)
  - Cleaning of equipment or facility
  - Environmental monitoring
Computer System Validation

- 21 CFR Part 11
- FDA 2002 Guide to Software Validation 2002
- MHRA 2015 Data Integrity Guidance
- EU Annex 11
- ISPE GAMP5
Part 11

- Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:
(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

(d) Limiting system access to authorized individuals.
Part 11 cont.

- (e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

- (f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

- (g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

- (h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.
23. INSPECTION CONSIDERATIONS

23.1 The attention paid by inspectors to the assessment of the GxP implications of computerised systems on a site (and between sites), will be determined to some extent by the overall *site history and risk assessment* carried out by the inspector in preparing for the inspection. Information computer technology management arrangements for the procurement and validation of software and systems may be centralised at the regulated user’s headquarter site rather than at the site of inspection. In such circumstances the controls, SOPs and records in place to ensure GxP compliance at inspection sites will need to be made available on site. In some circumstances it may also be necessary to consider an inspection at the HQ site.
23.2 Clearly where a site has a lot of automation and integrated computerised systems - and manufactures a range of sterile products - (for example), then the potential risks from a GxP failure, (whether computer related or otherwise) for the patient are high. However, where such automated systems are well designed, implemented, managed and controlled, then potential risks to product quality (and to patients) may be considerably reduced, compared with labour intensive operations, as the latter carry inherent risks from human variability and errors. Inspectors have to come to a judgement on this by studying the firm's evidence not just in relation to the technology aspects (through the application of GAMP etc.) but also the GxP risks identified (through PQ reports and such-like).

23.3 Humans design, build, test, implement and change these complex systems and there is opportunity for critical error with automated systems at any stage in the life-cycle unless properly managed. The GAMP Guide provides relevant guidance on these aspects.
23.8 It is essential that firms have a computerised systems validation policy together with linked SOPs and plans, including a listing, or inventory, of all their computerised systems - classified as to their use, criticality and validation status. For long standing systems, validation may have been carried out retrospectively and for systems purchased or implemented in the last few years, the validation should have been carried out (and recorded) prospectively. Firms should have plans to complete any outstanding retrospective validation of GxP related computer systems within a reasonable time period depending on the risks and complexity of the systems. The continued use of critical systems that are unsupportable by suppliers and cannot be validated must be justified by regulated users, supported by alternative fail-safe arrangements and considered for urgent phased replacement.

23.9 The firm's validation approach should follow a life-cycle methodology, with management controls and documentation as outlined in this guidance, which contains consensus best practice guidelines.
Summary

• If we develop a well designed process and understand how to monitor and control it.
• And if we automate all the required manufacturing steps such that our validated computer/automation systems can detect exceptions to the processing.
• And if all the computer system functionality is qualified/validated for its intended use.
• And if we ensure system changes/ overrides are readily detectable,
• Then we can limit our batch review to only exceptions that occur during processing.