DOCUMENTATION

Documentation is an essential part of the quality assurance system and, as such, should be related to all aspects of GMP. Its aim is to define the specifications for all materials and the method of manufacture and control, to ensure that all personnel concerned with manufacture have the information necessary to decide whether or not to release a batch of a drug for sale, and to provide an audit trail that will permit investigation of the history of any suspected defective batch. The specifications should describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Manufacturing formulae and processing and packaging instructions should specify all the starting materials used and describe all processing and packaging operations. Procedures should give directions for performing certain operations, e.g., cleaning, clothing, environmental control, sampling, testing, and equipment operation. Records should provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product.

Written records should be maintained so that data can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures should be established and followed for such evaluations and must include provisions for:

- A review of a representative number of batches, whether approved or rejected and, where applicable, the records associated with the batch.
- A review of complaints, recalls, and returned or salvaged drug products, and of the investigations conducted.

All documents related to the manufacture of intermediates, active pharmaceutical ingredients (API), and finished products should be prepared, reviewed, approved, and distributed according to written procedures. Such documents can be paper-based or in electronic form. Documents should be approved, signed, and dated by the appropriate responsible persons. No document should be changed without authorization and approval.

Each specification for raw materials, intermediates, final products, and packing materials should be approved and maintained by the quality control department. Periodic revisions of the specifications must be carried out whenever changes are necessary.

The issuance, revision, superseding, and withdrawal of all documents should be controlled, with maintenance of revision histories. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents. Superseded documents should be retained for a specific period of time.

Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

Documents should have unambiguous contents: the title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The process of reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.
All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

Documents should not be handwritten; however, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting. Sufficient space should be provided for such entries. Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

Data may be recorded by electronic data processing systems or photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions. Access should be restricted by passwords or other means and the result of entry of critical data should be independently checked. Batch records that are electronically stored should be protected by back-up transfer onto magnetic tape, microfilm, paper, or other means.

Specifications should be established and documented for raw materials, intermediates (where necessary), and API/formulations, as well as for labeling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or API/formulations that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.

If electronic signatures are used on documents, they should be authenticated and secure.

**Equipment cleaning and use record**

Records of major equipment use, cleaning, sanitization and/or sterilization, and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment and the name and signature of the person who has performed the cleaning and maintenance. The persons performing and double-checking the cleaning and maintenance should date and sign or initial the log, indicating that the work was performed. Entries in the log should be in chronological order.

Cross-contamination should be avoided by appropriate technical or organizational measures, for example:

- Production in segregated areas (required for products such as the penicillins, live vaccines, live bacterial preparations, and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning
- Providing appropriate air-locks and air extraction
- Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air
- Keeping protective clothing inside areas where products with special risk of cross-contamination are processed
- Using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination
- Using ‘closed systems’ of production
- Testing for residues and use of cleaning status labels on equipment

If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records of different activities like cleaning, maintenance, batch log, etc., are not necessary, provided the batch record
has complete traceability of this information. In case of formulation manufacturing, the appropriate cleaning procedure should be established to ensure removal of any residue of the previous product.

**Records of raw materials, intermediates, labeling, and packaging materials**

Records should be maintained, including:

- The name of the manufacturer; identity and quantity of each shipment of each batch of raw materials, intermediates, or labeling and packaging materials; the name of the supplier; the supplier's control number(s) (if known) or other identification number; the number allocated on receipt; and the date of receipt;
- The results of any test or examination performed and the conclusions derived from this;
- Records tracing the use of materials;
- Documentation of the examination and review of labeling and packaging materials for conformity with established specifications;
- The final decision regarding rejected raw materials, intermediates, or labeling and packaging materials.

Starting materials in the storage area should be appropriately labeled. Labels should bear at least the following information:

- The designated name of the product and the internal code reference, where applicable
- The batch number given by the supplier and, on receipt, the control or batch number (if any) given by the manufacturer; these must be documented so as to ensure traceability
- The status of the contents (e.g., on quarantine, on test, released, rejected, returned, recalled, etc.)
- Where appropriate, an expiry date or a date beyond which retesting is necessary

Master (approved) labels should be maintained for comparison with issued labels.

**Master production instructions/master production and control records (MPCR)/master formula card (MFC)**

To ensure uniformity from batch to batch, master production instructions for each intermediate or API/finished product should be prepared, dated, and signed by one person and independently checked, dated, and signed by a second person in the quality unit(s).

Competent persons experienced in production and quality control should be responsible for the content and distribution within the firm of instructions and master formulae. These should be duly signed and dated.

Outdated master formulae should be withdrawn but retained for reference. Copies of the master formula should be prepared in a manner that will eliminate any possibility of transcription error.

In certain circumstances, for example, in the first production runs following pilot development, the master formula might need to be amended. Any amendments must be formally authorized and signed by competent person(s). The amended document should be replaced at the earliest opportunity by a newly prepared master formula.

Processing should be carried out in accordance with the master formula. Master production instructions should include:

- The name of the intermediate/API/formulation being manufactured and an identifying document reference code, if applicable
- A complete list of raw materials and intermediates (designated by names or codes sufficiently specific to identify any special quality characteristics)
• An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included wherever justified.

• The production location and major production equipment to be used.

• Detailed production instructions, including the:
  1. Sequences to be followed
  2. Ranges of process parameters to be used
  3. The methods, or reference to the methods, to be used for preparing the critical equipment (e.g., cleaning, assembling)
  4. Sampling instructions and in-process controls, with their acceptance criteria, where appropriate
  5. Time limits for completion of individual processing steps and/or the total process, where appropriate
  6. Expected yield ranges at appropriate phases of processing or time.

• Where appropriate, special notations and precautions to be followed, or cross-references to these

• Instructions for storage of the intermediate or API/semi-finished formulations to assure its suitability for use; instructions should cover the labeling (specimen labels and packaging materials and special storage conditions with time limits, where appropriate).

**Batch production records/batch production and control records (BPCR)/batch manufacturing record (BMR)**

Batch production records should be prepared for each intermediate and API/formulation and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

Before any processing begins, a check should be performed and recorded to ensure that the equipment and workstation are clear of previous products, documents, or materials not required for the planned process and that the equipment is clean and suitable for use.

These records should be numbered with a unique batch or identification number and dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

The batch number should be immediately recorded in a logbook or by electronic data processing system. The record should include date of allocation, product identity, and size of batch.

Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

• Dates and, when appropriate, times
• Identity of major equipment used (e.g., reactors, driers, mills, etc.)
• Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
• Actual results recorded for critical process parameters
• Any sampling performed
• Signatures of the persons performing and directly supervising or checking each critical step in the operation
• In-process and laboratory test results
• Actual yield at appropriate phases or times
• Description of packaging and label
• Representative label (commercial supply)
• Any deviation noted, its evaluation, and investigation conducted (if appropriate) or reference to that investigation (if stored separately)
• Results of release testing
• All analytical records relating to the batch, or a reference that will permit their retrieval
• A decision for the release or rejection of the batch, with the date and signature of the person responsible for the decision
• The production record review

Production and quality control records should be reviewed as part of the approval process of batch release. Any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

The following information should be recorded at the time each action is taken (the date must be noted and the person responsible should be clearly identified by signature or electronic password):

• The name of the product, the batch number and the quantity of product to be packed, as well as the quantity actually obtained and its reconciliation
• The date(s) and time(s) of the packaging operations
• The name of the responsible person carrying out the packaging operation
• The initials of the operators of the different significant steps
• The checks made for identity and conformity with the packaging instructions, including the results of in-process controls
• Details of the packaging operations carried out, including references to equipment and the packaging lines used and, when necessary, instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area
• Whenever possible, the regular check for correctness of printing (e.g. batch number, expiry date and other additional overprinting) and specimen samples collected
• Notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person
• The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of product obtained; this is necessary to permit an adequate reconciliation.

**Laboratory control records**

Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

• A description of samples received for testing, including the material name or source, batch number and, where appropriate, the manufacturer and/or supplier; alternatively, other distinctive code, date of sample taken and, where appropriate, the quantity of the sample and date the sample was received for testing
• A statement of, or reference to, each test method used
• A statement of the weight or measure of sample used for each test as described by the method; data on, or cross-reference to, the preparation and testing of reference standards, reagents, and standard solutions
• A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, all properly identified to show the specific material and the batch tested
Complete records should also be maintained for:

- Any modifications to an established analytical method
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices
- All stability testing performed on APIs/formulations
- Out-of-specification (OOS) investigations

Complete records should be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions; record should also be maintained of periodic calibration of laboratory instruments, apparatus, gauges, and recording devices.

**Batch production record review**

Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units, following procedures approved by the quality unit(s).

All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

Distribution record should be maintained and must include the batch number; quantity produced; name, address, and contact details of customer; quantity supplied; and date of supply.