

CHAPTER 4 DOCUMENTATION

Principle

Good documentation constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, Manufacturing Formulae and instructions, procedures, and records must be free from errors and available in writing. The legibility of documents is of paramount importance.

General

- 4.1 *Specifications* 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, Processing and Packaging Instructions state all the starting materials used and lay down all processing and packaging operations.

Procedures give directions for performing certain operations e.g. cleaning, clothing, environmental control, sampling, testing, equipment operation.

Records 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.

- 4.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorisation dossiers.
- 4.3 Documents should be approved, signed and dated by appropriate and authorised persons.
- 4.4 Documents should have unambiguous contents; 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 reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.
- 4.5 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.
- 4.6 Documents should not be handwritten; although, 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.
- 4.7 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.
- 4.8 The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable. They should be retained for at least one year after the expiry date of the finished product.

- 4.9 Data may be recorded by electronic data processing systems, 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 authorised 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 electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that the data are readily available throughout the period of retention.

Documents required

Specifications

- 4.10 There should be appropriately authorised and dated specifications for starting and packaging materials, and finished products; where appropriate, they should be also available for intermediate or bulk products.

Specifications for starting and packaging materials

- 4.11 Specifications for starting and primary or printed packaging materials should include, if applicable:
- a) a description of the materials, including:
 - the designated name and the internal code reference;
 - the reference, if any, to a pharmacopoeial monograph;
 - the approved suppliers and, if possible, the original producer of the products;
 - a specimen of printed materials;
 - b) directions for sampling and testing or reference to procedures;
 - c) qualitative and quantitative requirements with acceptance limits;
 - d) storage conditions and precautions;
 - e) the maximum period of storage before re-examination.

Specifications for intermediate and bulk products

- 4.12 Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

- 4.13 Specifications for finished products should include:
- a) the designated name of the product and the code reference where applicable;
 - b) the formula or a reference to;
 - c) a description of the pharmaceutical form and package details;
 - d) directions for sampling and testing or a reference to procedures;
 - e) the qualitative and quantitative requirements, with the acceptance limits;
 - f) the storage conditions and any special handling precautions, where applicable;
 - g) the shelf-life.

Manufacturing Formula and Processing Instructions

Formally authorised Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

4.14 The Manufacturing Formula should include:

- a) the name of the product, with a product reference code relating to its specification;
- b) a description of the pharmaceutical form, strength of the product and batch size;
- c) a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material; mention should be made of any substance that may disappear in the course of processing;
- d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.15 The Processing Instructions should include:

- a) a statement of the processing location and the principal equipment to be used;
- b) the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);
- c) detailed stepwise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);
- d) the instructions for any in-process controls with their limits;
- e) where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;
- f) any special precautions to be observed.

Packaging Instructions

4.16 There should be formally authorised Packaging Instructions for each product, pack size and type. These should normally include, or have a reference to, the following:

- a) name of the product;
- b) description of its pharmaceutical form, and strength where applicable;
- c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
- e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;
- f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
- g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- h) details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Records

- 4.17 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. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

Before any processing begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use.

During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations:

- a) the name of the product;
- b) dates and times of commencement, of significant intermediate stages and of completion of production;
- c) name of the person responsible for each stage of production;
- d) initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);
- e) 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);
- f) any relevant processing operation or event and major equipment used;
- g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
- h) the product yield obtained at different and pertinent stages of manufacture;
- i) notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions.

Batch Packaging Records

- 4.18 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions and the method of preparation of such records should be designed to avoid transcription errors. The record should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

Before any packaging operation begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

- a) the name of the product;
- b) the date(s) and times of the packaging operations;
- c) the name of the responsible person carrying out the packaging operation;
- d) the initials of the operators of the different significant steps;
- e) records of checks for identity and conformity with the packaging instructions including the results of in-process controls;
- f) details of the packaging operations carried out, including references to equipment and the packaging lines used;

- g) whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
- h) notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;
- i) 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 obtained product, in order to provide for an adequate reconciliation.

Procedures and records

Receipt

- 4.19 There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material.
- 4.20 The records of the receipts should include:
- a) the name of the material on the delivery note and the containers;
 - b) the "in-house" name and/or code of material (if different from a);
 - c) date of receipt;
 - d) supplier's name and, if possible, manufacturer's name;
 - e) manufacturer's batch or reference number;
 - f) total quantity, and number of containers received;
 - g) the batch number assigned after receipt;
 - h) any relevant comment (e.g. state of the containers).
- 4.21 There should be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

Sampling

- 4.22 There should be written procedures for sampling, which include the person(s) authorised to take samples, the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality (see Chapter 6, item 13).

Testing

- 4.23 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded (see Chapter 6, item 17).

Other

- 4.24 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by the Qualified Person(s) in accordance with the requirements of Article 51 of Directive 2001/83/EC¹.
- 4.25 Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary (see Chapter 8).

¹ Article 55 of Directive 2001/82/EC

- 4.26 There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for:
- validation;
 - equipment assembly and calibration;
 - maintenance, cleaning and sanitation;
 - personnel matters including training, clothing, hygiene;
 - environmental monitoring;
 - pest control;
 - complaints;
 - recalls;
 - returns.
- 4.27 Clear operating procedures should be available for major items of manufacturing and test equipment.
- 4.28 Log books should be kept for major or critical equipment recording, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.
- 4.29 Log books should also record in chronological order the use of major or critical equipment and the areas where the products have been processed.