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4 Guideline on manufacture of the finished dosage form

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8 This guideline replaces the “Note for Guidance on Manufacture of the Finished Dosage Form”
9 (CPMP/QWP/486/95)

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Guideline on manufacture of the finished dosage form

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Executive summary

This guideline replaces the note for guidance on the manufacture of the finished dosage form (CPMP/QWP/486/95). The note for guidance has been updated to reflect changes to the format and content of the Common Technical Document (CTD) Module 3 dossier. It also addresses current manufacturing practices in terms of complex supply chains and worldwide manufacture. In addition, the content and principles of the ICH Q8 guideline (ref 1) is also taken into account.

This guideline does not introduce new requirements on authorised medicinal products for human use. However as stated in article 23 of Directive 2001/83/EC (ref 2) after an authorisation has been issued, the authorisation holder must, in respect of the methods of manufacture and control take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

1. Introduction (background)

The objective of the guideline on the manufacture of the finished dosage form is to provide clarification on the type and level of information that should be included in the CTD Module 3 of the marketing authorisation application (MAA) dossier with respect to the manufacturing process description. This description should include information about critical steps and intermediates and provides a link between the pharmaceutical development, the proposed control strategy and process validation. The guideline also addresses aspects related to increased outsourcing and new manufacturing practices such as complex manufacturing chains or issues with prolonged holding times and transportation conditions. Detailed information about requirements of sterilisation processes is provided in a separate guideline.

2. Scope

This guideline is applicable to the manufacture of the finished dosage form of chemical and herbal medicinal products for human use intended for marketing authorisation. It also applies to variations for authorised products in cases where changes to the manufacturing process affecting the MA are proposed.

The principles described are in general also applicable to biological medicinal products. Due to the nature of advanced therapy medicinal products (ATMPs), the guideline is not applicable to these.

This guideline does generally not apply to radiopharmaceuticals; however, the principles of this guideline may be applied where relevant.

Application of this guideline to the manufacture of investigational medicinal products is not intended, but the principles of this guideline may be applied.

3. Legal basis

This guideline should be read in conjunction with Directive 2001/83/EC Article 8.3 (d) (ref 2) where it is stated that the application for a marketing authorisation shall contain a description of the manufacturing method.

The requirements on the description of the manufacturing method in the CTD Module 3 of marketing authorisation dossier are described in Annex 1, Part 1 (section 3.2.2.3) to this Directive and will be further elaborated in this guideline.

4. Manufacture

The headings of this guideline follow the structure of the CTD format Module 3, Section 3.2.P.3 Manufacture.

Only product specific aspects of manufacture need to be described and included in the MA-dossier; general elements of Good Manufacturing Practice (GMP), (ref 3) should not be included.

4.1. Manufacturer(s)

For each stage of the manufacturing process (including the assembly and testing), details should be given of all the individual sites involved (including those from the same company). The name, address and responsibility of each manufacturer, including contractors should be provided.

The company responsible for the final release of the product onto the market shall be specified. Only those sites that are involved in the manufacture and control of finished product until release need to be included.

4.2. Batch Formula

The batch formula for the intended batch size should be stated. In case a range of batch sizes is proposed, the batch formula should be provided for at least the highest and lowest batch sizes.

An application for a range of batch sizes should be adequately justified taking into account the guidance provided in the guideline on process validation (ref 4).

If the bulk product is assembled into different presentations or packs, the production batch size should be defined by the original bulk before any division. When the length of the subsequent processes and assembly is considered critical (e.g. filling for aseptically manufactured products), the division pattern should be indicated.

The batch size for a product to be marketed should normally be compatible with qualified industrial equipment. It should be sufficient enough to allow process capability to be established. For example, a commercial batch size for solid oral dosage forms should be at least 100,000 units unless justification is provided (e.g. orphan drugs).

If sub-batches are prepared and combined for subsequent processing, their formulae and the number of sub-batches per intended batch size should be stated. In addition, if a batch is sub-divided towards the end of the process to reflect equipment processing capability, this should be clearly indicated. The number of sub-batches per intended batch size should be justified.

In case of continuous manufacture, the information about batch size in traditional terms might not be relevant; however information how a batch is defined should be provided. The expected size of one campaign (e.g. period of time) should be stated.

The names, quantities and reference to the quality standards of all ingredients used in the course of the manufacture should be stated. This includes ingredients which are removed from the product during the production process, such as granulation liquids, solvents and gases.

Ingredients that may not always be used should also be mentioned, such as acids and alkalis for pH adjustment. Overages must be clearly indicated in quantitative terms and justified in the pharmaceutical development section of the dossier.

In justified cases, upper and lower acceptance limits for the actual quantity of each ingredient could be stated.

When the quantity of an active ingredient to be used is calculated from the actual assay value of the batch of that active ingredient ("factorisation"), this should be stated and justified. If another ingredient is used to keep the total mass per batch equal to the quantity provided for in the batch manufacturing formula, this should also be indicated.

4.3. Description of Manufacturing Process and Process Controls

General aspects

A narrative description of the full manufacturing process should be provided, accompanied by a flow chart describing each step of the process with respective in-process controls where relevant and showing at each stage where materials enter the process. In case a Design Space is proposed, this should be presented in a transparent manner.

It is important that the process descriptions are comprehensive, suitably detailed and describe process steps in a sequential manner including batch size(s) and equipment type(s) and size(s) where appropriate. In case of continuous manufacturing, the description of manufacturing process is expected to be provided in the same way. Emphasis should be given on frequency of in-process controls and it should be clearly stated when the release testing is performed.

The manufacturing process description should be adequately justified by development, in particular any process operating conditions or ranges. In addition, and where relevant, any required environmental conditions during manufacture should be stated e.g. low humidity for an effervescent tablet.

The steps and points at which process controls, intermediate tests or final product controls are conducted should be identified. To make the process fully understandable and to allow assessment of the validity of the process validation studies/ validation protocol to support the claimed manufacturing process, all steps in the process should have the necessary detail in terms of appropriate process parameters along with their target values or ranges.

The description of a manufacturing process with wide acceptance ranges (or described only by an upper or lower limit), generally requires a more thorough discussion and/or scientific rationale in the manufacturing process development section.

In some more complex cases (e.g. biotech products, use of models for process control, continuous manufacturing processes), information of how accidental deviations from the approved manufacturing process will be managed can be helpful to assure that the intended quality of the product is retained.

Full scale manufacturing process validation is not requested at the time of application for certain types of products (ref 4). If the result of such full scale study is not available at the time of submission, it is expected that process parameters' settings identified during manufacturing process development are laid down in the process description. In the event that any changes are required to the registered process parameters as a result of full scale process validation studies, then these changes should be sought post approval by way of variation, in accordance with the variation Regulation (ref 5, 6).

Every drug product manufacturing process (including manufacturing durations, hold times and conditions during transport) has an associated control strategy. The control strategy should be outlined based on development studies. Consideration should be given to what extent the assurance of quality is founded on the manufacturing process itself. The significance of the process description and process controls as part of the overall control strategy should be evaluated. It is expected that different control strategies may be utilised in case real time release testing (RTRT) (ref 7) is proposed, a design space is claimed (ref 1) or a standard manufacture is performed. Possible elements of the control strategy are described in the glossary of ICH Q8 (ref 1) and Q10 (ref 8).

Expected level of detail in the manufacturing process description

Though it is expected that process description is considered in relation to other elements of the control strategy (ref 1), there is a need to describe the manufacturing process in relevant detail since consistent quality of a product cannot be safeguarded by end product testing.

The same requirements apply to the level of detail in the manufacturing process description irrespective of the development approach, i.e. if the product has been developed by the traditional or enhanced approach (ref 1).

The operating principle for the equipment used should be described for each unit operation. The type of equipment should generally be stated (general reference to “suitable equipment” is not acceptable). The critical steps and points at which process controls, intermediate testing or final product controls are conducted should be clearly identified. Steps in the process should have the necessary detail in terms of appropriate process parameters along with their target values or ranges (general reference to “typically” set points is not acceptable). The process parameters included in the manufacturing process description should not be restricted to the critical ones; all parameters that have been demonstrated during development as needing to be controlled or monitored during each unit operation, to ensure that the output from a processing step and also that the final product is ultimately of the intended quality need to be described. Details of non-critical process parameters should also be included at an appropriate level of detail to at least give a standard/basic description of relevant steps.

An example of what type of details should be included in the manufacturing description is presented in the annex.

Technical adaptations in the manufacturing process

It would generally be expected that regardless of the number of finished product manufacturing sites proposed, essentially the same manufacturing process would be followed for a specific medicinal product. However, some technical adaptations might be necessary, if more than one manufacturer or manufacturing site for the drug product is foreseen. Depending upon equipment availability, different pieces of equipment could be used for the same manufacturing processing step. The following examples illustrate the possible use of technical adaptations for different manufacturing processing steps.

Solid oral dosage forms

Different equipment can be used for:

- Wet granulation (wet granulation by high shear -, low shear - or fluid bed granulation);
- Granule drying (e.g. fluid bed-, tray drying, one pot (high shear granulation/drying) systems);
- Dry granulation (roller compaction or slugging);
- Sizing/delumping (e.g. oscillating -, rotating - or hammer mill);

- Coating (e.g. pan coating, fluidized bed coating);
- Dry blending (e.g. high shear blender, IBC blender, conical screw blender, V blender); and
- Tablet compression on a fully instrumented or manually controlled tablet press.

Liquid dosage forms

Preparation of solutions can be performed in simple stainless steel tanks equipped with a stirrer and/or homogeniser or in advanced mixing/homogenising equipment which can be run under vacuum.

Where technical adaptations are proposed in the manufacturing process, the use of such adaptations should be fully justified and supported by evidence, showing that all steps proposed will consistently produce any intermediate and finished product that comply with the in process controls and the product specifications. Irrespective of differences in the manufacturing process, the final drug product should be characterised by one release and one shelf-life specification.

Where relevant, the justified technical adaptations in various manufacturing steps in the manufacturing process of one or more manufacturers and corresponding in-process controls should also be transparently shown in separate flow-charts, which, if applicable, should also include all adaptations. On presentation of separate flow-charts in a dossier the different manufacturing steps should be listed and the adaptations should be compared to each other by the applicant. The applicant should justify that adaptation, on the basis of using different equipment, do not have any significant influence on the drug product quality and this should be supported by data. The in-process controls and corresponding acceptance limits should also be described, when relevant. Where any differences are proposed at different manufacturing sites, the information should always be presented in the same module 3 section document, but if required differentiated based upon the actual manufacturing site.

In contrast to technical adaptations as described above, truly alternative manufacturing processes, which use different principles and may or may not lead to differences in the in-process control and/or drug product quality are not acceptable (e.g. using different sterilisation procedures – terminal sterilisation of end product vs. aseptic manufacture using sterile filtration – possibly to reflect the use of different containers with different heat resistance properties; wet granulation vs. dry granulation).

4.4. Controls of Critical Steps and Intermediates

All critical steps and intermediates isolated during the manufacture of the finished drug product should be listed in this section including details about the sampling strategy, applied test methods and acceptance criteria. The fact that a process parameter is controlled and verified to be within a range that does not affect a critical quality attribute (CQA) does not make it non-critical by default. While the risk is reduced the monitoring with its established acceptance criteria should be included in the description to assure a sufficient regulatory oversight. The justification for the identification of steps as critical or non-critical should be provided including link to experimental data in pharmaceutical development (e.g. risk assessment table) if applicable.

Bulk storage

A manufacturing process generally involves a series of sequential processing steps, where the output from one step is isolated before it is incorporated into the next processing step, possibly after some confirmatory testing of quality. Any isolated material can therefore be considered as bulk and depending upon the dosage form and proposed manufacturing facilities and arrangements, the bulk (multiple bulks possible in a single process) may be stored and as necessary transported in a suitable

container before further processing. Therefore, bulk storage is any stage in the manufacturing process of any pharmaceutical product where bulk is held in storage prior to further processing e.g. bulk solution prior to filling, granulates, uncoated tablets etc.

It should be stated whether any bulk product is to be stored and if so, under which conditions. The maximum holding times of bulk product should be stated and appropriately supported by data (e.g. challenging the maximum hold time in process validation studies or by providing dedicated stability studies for the bulk storage). In addition, where relevant, the maximum processing times of both individual and a combination of processing steps (e.g. from the start of manufacture to packaging for aseptic processing) should be appropriately supported. The reasons for any prolonged storage/processing times should be stated and be consistent with GMP. Although not defined anywhere, as a general rule, prolonged storage means more than 30 days for solid oral dosage forms and more than 24 hours for sterile products.

Where relevant, stability data to support the holding time should be provided (on at least two pilot scale batches). The stability studies should be performed at relevant temperature and humidity with regards to the expected bulk storage conditions (if relevant temperature and humidity during storage does not correspond with ICH condition, other conditions should be used).

In case of bulk storage, the product shelf-life should be calculated according to the Note for Guidance on the start of shelf-life of the finished dosage form (ref 9). If other approaches to calculate shelf life are proposed, these should be declared and justified through inclusion of batches that represent the full proposed holding intervals of the bulk product (intermediate) in the finished product stability program.

Transportation of bulk between manufacturing sites should be explained and justified. The principles of the guideline on Good Distribution Practice (ref 10) and guidance given in GMP Annex 15 on transport should be taken into consideration. The impact of short or longer excursions outside of the original storage conditions should be discussed and, where necessary, supported by accelerated stability data.

The suitability of the proposed bulk container closure system should be justified. The type and level of information required will depend on the nature of the bulk product. The materials of the bulk container closure system should be described in the dossier and its control specification stated.

4.5. Process Validation and/or Evaluation

Description, documentation, and results of the validation and/or evaluation studies should be provided in this section. For more details see Process Validation guideline (ref 4)**.**

Definitions (ref 1)

Control Strategy:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Critical Process Parameter (CPP):

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Critical Quality Attribute (CQA):

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Design Space:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Real Time Release Testing:

The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.

References

1. ICH Q8 (R2) (Pharmaceutical development), EMA/CHMP/ICH/167068/2004;
2. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use;
3. Eudralex volume 4 (GMP guidelines);
4. Guideline on process validation for finished products - information and data to be provided in regulatory submissions EMA/CHMP/CVMP/QWP/BWP/70278/2012 Rev. 1;
5. Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products;
6. Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures;
7. Guideline on Real time release testing EMA/CHMP/QWP/811210/2009-Rev1;
8. ICH Q10 (Pharmaceutical quality system). EMA/CHMP/ICH/214732/2007;
9. Note for guidance on the start of shelf-life of the finished dosage form CPMP/QWP/072/96 / EMEA/CVMP/453/01;
10. Guideline on Good Distribution Practice of medicinal products for human use 2013/C 343/01.

Annex

Example of a manufacturing process description: expected level of detail

Drug product: 200 mg tablet

Process step: wet granulation

Operating principle: high shear granulation

Equipment type: vertical impeller geometry (bottom driven), 600 L capacity

Non exhaustive list of process parameters which should be considered:

- Delumping sieve size.
- Mixing time for binder solution.
- Mixing speed for binder solution.
- Fill volume.
- Premix time.
- Premix impeller speed.
- Premix chopper speed.
- Binder solution pressure.
- Binder solution feed pump speed.
- Binder solution flow rate.
- Binder solution total amount.
- Impeller rotation speed for the different granulation phases.
- Chopper rotation speed for the different granulation phases.
- Wet massing time.
- Bowl temperature.
- Product temperature.
- Wet mass screen size.

List of parameters that have been demonstrated during development as needing to be controlled or monitored during the unit operation:

- Fill volume.
- Premix time.
- Binder solution flow rate.
- Binder solution total amount.

- Impeller rotation speed for the different phases.
- Chopper rotation speed for the different phases.
- Wet massing time.
- Wet mass screen size.

Narrative description:

1. Weigh and delump the required amount of drug substance and intra-granular excipients.
2. Weigh the required amount of binder excipient and purified water; charge the purified water in a mixing vessel and dissolve the binder excipient; mix until a clear solution is obtained.
3. Load Drug substance, intra-granular excipient 1, intra-granular excipient 2 and intra-granular excipient 3 in the bowl of the high shear mixer granulator. Target fill volume: 30% w/v (180 kg).
4. Mix the dry material for 2 minutes (target impeller speed: 95 rpm; chopper off).
5. Wet the dry mix (from step 4) with the binder solution (from step 2) added by fine atomization through a binary nozzle at a target rate of 9 kg/min for 3 minutes (total amount added: 27 kg (15% w/w); target impeller speed: 95 rpm; chopper off).
6. Wet mass the blend for 5 minutes with impeller (target impeller speed: 172 rpm; chopper speed: 2000 rpm).
7. Screen the wet mass through in-line sizing mill unit of 1 mm and transfer to fluid bed dryer.

Description of the manufacturing process (traditional application):

Process step #	Parameter	Target value
3/ Loading	Fill volume	30% w/v (180 kg)
4/ Pre mixing	Time	2 minutes
5/ Binder solution addition	Flow rate	9 kg/min
	Total amount	15% w/w (27 kg)
	Impeller speed	95 rpm
	Chopper speed	0
	Time	3 minutes
6/ Wet massing	Impeller speed	172 rpm
	Chopper speed	2000 rpm
	Time	5 minutes
7/ Wet mass screening	Screen size	1 mm

Description of the manufacturing process (QbD application):

Process step #	Parameter	Criticality	Target value or range
3/ Loading	Fill volume	Non CPP	25 – 35% w/v (151 – 209 kg)
4/ Pre mixing	Time	Non CPP	1 – 3 minutes
5/ Binder solution addition	Flow rate	Non CPP	5 – 15 kg/min
	Total amount	CPP	12 – 18% w/w (22 – 32 kg)
	Impeller speed	Non CPP	80 – 110 rpm
	Chopper speed	Non CPP	0
	Time	Non CPP	2 – 4 minutes
6/ Wet massing	Impeller speed	CPP	155 – 189 rpm
	Chopper speed	CPP	1800 – 2500 rpm
	Time	CPP	3 – 7 minutes
7/ Wet mass screening	Screen size	Non CPP	0.595 – 1.41 mm

To note:

- Same level of detail whatever the type of application (traditional or enhanced pharmaceutical development);
- Operating principle described;
- Equipment type / capacity described;
- Critical and non-critical process parameters described (with target values or ranges) leading to a comprehensive description of the unit operation;
- Reduced list of process parameters remaining in the description compared to the initial list; the following has been taken into account:
    - Nature of the drug substance (e.g. the drug substance is chemically stable thus no need to describe the environmental and product temperatures);
    - Degree of complexity of the dosage form (e.g. the tablet is highly dosed thus no need to describe in details the pre mixing step);
    - Degree of complexity of the process (e.g. the delumping of raw materials before processing is not an important step thus no need to describe the delumping sieve size; the preparation of the binder solution is a straight forward operation which is merely monitored by the visual control of the final solution thus no need to describe the mixing parameters; the binder solution addition is adequately summarized by the output “flow rate” thus no need to describe the liquid pressure and the pump speed). Regarding the delumping operation and the binder solution preparation, none of the critical quality attributes (CQAs) of the intermediate product or the final product is dependent on these operations. For this reason also, the description does not include process parameters for these operations.