EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 July 2017
EMA/CHMP/QWP/245074/2015
Committee for Human Medicinal Products (CHMP)

Guideline on manufacture of the finished dosage form

Draft agreed by QWP, BWP	February 2015
Adopted by CHMP for release for consultation	23 April 2015
Start of public consultation	09 July 2015
End of consultation (deadline for comments)	09 January 2016
Agreed by QWP	May 2017
Agreed by BWP	June 2017
Endorsed by HMPC	18 July 2017
Adopted by CHMP	20 July 2017
Date for coming into effect	6 months after publications

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

Keywords	***Manufacture, finished product, process description, level of detail, technical adaptation, intermediate, bulk, storage, transport, CTD***

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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 the requirements as laid down in the current legislation Directive 2001/83/EC, and to follow 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) are 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, after a marketing authorisation (MA) has been approved, the authorisation holder should, 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 controlled 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 outsourcing and new manufacturing practices such as complex manufacturing chains or issues with prolonged holding times and transportation conditions. Detailed information about requirements of the sterilisation process 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. Where relevant, the principles of this guideline may also be applied to radiopharmaceuticals and to chemical investigational medicinal products.

3. Legal basis

This guideline should be read in conjunction with Directive 2001/83/EC Article 8.3 (d), as amended 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. Further details on the information to be provided are outlined 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 packaging, 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. This applies also to all quality control sites, including on-going stability testing if different from the manufacturing site(s).

The EU site responsible for batch release in the EU market should be specified.

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 range should be stated and the batch formula should be provided for at least the largest and smallest batch sizes.

An application for a range of batch sizes should be adequately justified as not adversely impacting the critical quality attributes (CQAs) of the finished product in accordance with 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 bulk before any division. When the length of the subsequent processes and assembly is considered critical (e.g. filling time for aseptically manufactured products), the worst-case scenario of the division pattern (e.g. in respect of total filling time) should be indicated.

The batch size for a product to be marketed should normally be compatible with production scale equipment. It should be sufficiently large to be representative of commercial manufacturing to enable demonstration of a state of control. 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 medicinal products) (ref. 4).

If sub-batches are prepared and combined for subsequent processing, this should be justified as the final batch is required to be homogeneous, 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 (e.g. solid dosage form manufacture where sub lots are required due to equipment capacity). The number of sub-batches per intended batch size should be stated.

In case of continuous manufacture, the information about batch size in traditional terms might not be relevant; however, information as to how a batch is defined should be provided (e.g. expressed in terms of a period of time or a quantity of product, and may be expressed as ranges).

The names, quantities and reference to the quality standards of all ingredients used in the course of the manufacture should be stated. Ingredients which are removed from the product during the production process, such as granulation liquids, solvents and gases should be included but their quantities may be expressed as ranges.

Ingredients that are optionally used, such as acids and alkalis for pH adjustment, should also be mentioned. Formula overages must be clearly indicated in quantitative terms and justified in the pharmaceutical development section of the dossier. Upper and lower acceptance limits for the actual quantity of each ingredient may be stated in the batch formula; however, the proposed acceptance limits should be justified. 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 including in-process controls and showing at each stage where materials enter the process. In case a design space is proposed, this should be clearly identified and described.

The manufacturing process description should be adequately justified in 3.2.P.2 by development data, in particular as regards any process operating conditions or ranges. The description of a manufacturing process with wide ranges (wider than would normally be accepted as normal operating 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.

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, these changes should be applied for via post approval variation, in accordance with the variation Regulation (ref. 5, ref. 6).

Where specifically relevant for the product, any required environmental conditions during manufacture should be stated e.g. low humidity for an effervescent tablet.

Depending on the nature of the process and the product (e.g. sterile products), manufacturing durations of critical steps and hold times should be stated and justified.

The steps at which process controls, intermediate tests or final product controls are conducted should be identified.

Consideration should be given in 3.2.P.2 to what extent the assurance of quality of the finished product 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 outlined based on development studies and evaluated. Indeed, every finished product manufacturing process should have an associated control strategy suitable for its intended purpose. 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), a continuous manufacture or a standard manufacture is performed.

Expected level of detail in the manufacturing process description

Although it is expected that the process description is considered in relation to 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 alone.

It is important that the process description is comprehensive, including process steps in a sequential manner with batch size(s), operating principle and equipment type(s) for each unit operation (mere reference to “suitable equipment” is not sufficient; conversely, details such as the serial number and model are not required). Equipment working capacity should be stated where appropriate. To make the process fully understandable and to allow assessment of the validity of the process, steps in the process should have the necessary detail in terms of appropriate process parameters along with their target values or ranges (mere reference to “typical” set points is not acceptable). Where criticality is assigned to process parameters, the description of the process parameters should not only be restricted to CPPs, but also to those parameters important for manufacturing process consistency. Non-critical process parameters and also parameters for which the impact on quality attribute cannot be ruled out and which are considered to be important for the execution and/or the consistent performance of any particular process step, and consequently its output, should be described at an appropriate level of detail. A well described manufacturing process is essential to understand what is critical and what is supportive. Any information which is considered to be purely supportive should be justified and clearly identified.

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 minimal (traditional) or enhanced approach.

In case of continuous manufacturing, the description of manufacturing process is expected to be provided in the same way.

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 should be applied for a specific medicinal product. However, some technical adaptations might be necessary if more than one manufacturer or manufacturing site for the finished product is foreseen. Technical adaptations are equally acceptable within a manufacturer/ manufacturing site given appropriate justification. Depending upon equipment availability, different types of equipment could be used for the same manufacturing processing step.

Where technical adaptations are proposed in the manufacturing process, these 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 any differences in the manufacturing process, the finished product should comply with the same release and shelf-life specifications.

Where relevant, the justified technical adaptations in various steps of the manufacturing process of one or more manufacturers and corresponding in-process controls should also be transparently shown

in separate flow-charts. 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 the adaptation, on the basis of using different types of equipment, does not have any significant influence on the finished product quality and this should be supported by data. The in-process controls and corresponding acceptance limits should also be described. Where any technical adaptations are proposed at different manufacturing sites, the information should always be presented in the same Module 3 section, but if required differentiated for each manufacturing site.

The following examples illustrate the possible use of technical adaptations for different manufacturing processing steps.

Liquid dosage forms

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

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

In contrast to technical adaptations as described above, alternative manufacturing processes, which use different principles and may or may not lead to differences in the in-process control and/or finished 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; or wet granulation vs. dry granulation).

4.4. Controls of Critical Steps and Intermediates

All critical steps and intermediates identified during the manufacture of the finished product should be listed in this section including any in-process controls, applied test methods and acceptance criteria.

For complex control strategies (e.g. use of models for process control, continuous manufacturing), emphasis should be given on the frequency of in-process controls and it should be clearly stated how release testing and product release decisions are made. Information of how unexpected deviations from the approved manufacturing process would be detected and managed should be provided to assure that the intended quality of the product is retained.

The fact that a process parameter in a manufacturing step 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, monitoring with 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 a link to experimental data in the pharmaceutical development section (e.g. risk assessment table), if applicable.

Storage of intermediate and bulk products

An intermediate product is defined as partly processed material that must undergo further processing steps before it becomes bulk product e.g. solution prior to filling, granulates, uncoated tablets etc.

A bulk product is defined as any product which has completed all processing steps, up to but not including, final packaging.

A manufacturing process generally involves a series of unit operations, where intermediate product is processed to become bulk product.

In some cases, the intermediate may be stored, and if necessary, transported in a suitable container before further processing. It may also be subject to confirmatory testing prior to further processing to confirm that quality attributes have not changed and therefore any additional testing details should be provided. Hold time validation for the storage of intermediate product is a GMP matter and normally need not be presented routinely in the application for a marketing authorisation. However, some specific types of products (e.g. sterile products, biological products) may require presentation of data relevant to the type of product and this should be taken into consideration depending on the characteristics of that particular product.

It should be stated whether storage is required before final packaging and if so, under what temperature, humidity or other environmental conditions. The level of information to be provided in the documentation is dependent on the nature of the bulk product.

Where relevant, the maximum holding times of the bulk product or, alternatively, the maximum batch manufacturing time from start of product manufacture to completion of packaging into the final primary container for marketing should be stated, appropriately justified and supported by data in relevant parts of the dossier (e.g. challenging the maximum hold time in process validation studies or providing dedicated stability studies for the bulk storage).

The reasons for any prolonged storage/processing times should be stated and be consistent with GMP. Time limits for processing should be minimised and limits should be justified and appropriate to ensure product quality. 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).

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 the start of shelf life are proposed, these should be described and justified by the inclusion of supporting data from batches that represent the full proposed holding time of the bulk product (intermediate) in the finished product stability program.

For transportation of bulk product (intermediate) between manufacturing sites guidance is given in GMP Annex 15 on how transport should be taken into consideration. The impact of short or longer

excursions outside of the original storage conditions should be discussed, where necessary, supported by accelerated or real time stability data.

The suitability of the proposed bulk product (intermediate) container closure system for bulk storage (and transport if relevant) should be justified in relevant parts of the dossier. The materials used for the bulk container closure system should be described along with the control specification for primary bulk packaging.

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

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 (ref. 8).

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 (ref. 1).

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 (ref. 1).

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 (ref. 1).

Hold Time:

Hold time can be considered as the established time period for which materials (dispensed raw materials, intermediates and bulk dosage form awaiting final packaging) may be held under specified conditions and will remain within the defined specifications (ref. 11).

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 (ref. 1).

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;
11. Supplementary guidelines on GMP: General guidance on hold-time studies. In: WHO Expert, Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 4 (WHO Technical Report Series, No. 992)

Annex

The following example of manufacturing process description aims at clarifying the regulatory expectations in terms of level of detail. It is proposed as an illustration of what could be provided in a dossier, depending on the development approach followed. The process parameters listed are for guidance purposes and not mandated. Process description should always be considered case by case, and should be filed according to the individual manufacturing process as developed and validated.

To explain the description presented in Section 3.P.3.3 (starts with **Narrative description**), some elements from manufacturing process development are reproduced below:

Finished product: 200 mg tablet

Process step: granulation

Operating principle: wet high shear granulation

Equipment type: vertical high shear granulator

Non exhaustive list of process parameters possibly considered during development ("early development list"):

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

This early development list is not expected to be provided in the dossier, unless a formal risk assessment of the process is claimed, but is meant to emphasize that many more parameters are

considered during development than those presented in the following reduced list, which is retained in the process description.

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

- Fill volume.
- Premix time.
- Granulation solution flow rate.
- Granulation solution amount.
- Impeller rotation speed for the different phases.
- Chopper rotation speed for the different phases.
- Wet massing time.
- Wet mass screen size.

Section 3.2.P.3.3

Narrative description (common to minimal (traditional) and to enhanced development approaches):

1. Weigh and delump the required amount of active 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 active substance, intra-granular excipient 1, intra-granular excipient 2 and intra-granular excipient 3 in the bowl of the high shear mixer granulator.
4. Mix the dry material.
5. Wet the dry mix (from step 4) with the granulation solution (from step 2) added by fine atomization through a binary nozzle.
6. Wet mass the blend with impeller.
7. Screen the wet mass through in-line sizing mill unit and transfer to fluid bed dryer.

Process parameters settings (minimal development approach):

Process step #	Parameter	Target value or range
3/ Loading	Fill volume	30% w/v
4/ Pre mixing	Time	2 minutes (1 – 3 minutes)
5/ Granulation solution addition	Flow rate	9 kg/min

	Granulation solution amount[#]	15% w/w
	Impeller speed	90 rpm
	Chopper speed	0
	Time	3 minutes (2 – 4 minutes)
6/ Wet massing	Impeller speed	170 rpm
	Chopper speed	2000 rpm
	Time	5 minutes (4 – 6 minutes)
7/ Wet mass screening	Screen size	1 mm

[#]The quantity of water to be used is calculated as a percentage of the total weight of the dry components of the inner phase (intra-granular components). Water is removed during processing.

Process parameters settings (enhanced development approach):

Process step #	Parameter	Criticality	Target value or range (*)
3/ Loading	Fill volume	Non CPP	30 – 50% w/v
4/ Pre mixing	Time	Non CPP	1 – 3 minutes
5/ Granulation solution addition	Flow rate	Non CPP	5 – 15 kg/min
	Granulation solution amount[#]	CPP	12 – 18% w/w
	Impeller speed	Non CPP	80 – 110 rpm
	Chopper speed	N/A	0
	Time	Non CPP	2 – 4 minutes
6/ Wet massing	Impeller speed	CPP	150 – 190 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

*Ranges established on the basis of multivariate evaluation.

[#]The quantity of water to be used is calculated as a percentage of the total weight of the dry components of the inner phase (intra-granular components). The absolute volume of water used may vary between 12 and 18% w/w, implying a variable binder concentration in the granulation solution over this range. Water is removed during processing.

Notes for the above examples:

- The same basic requirements apply to the level of detail provided in terms of the manufacturing processing steps and parameters listed in section 3.2.P.3.3 whatever the approach to pharmaceutical development (minimal or enhanced). However, depending upon the level of process understanding that has been gained during development and also the control strategy, the way the information is presented may be slightly different and the manufacturing process will reflect any justified and supported flexibilities when an enhanced development approach has been followed (e.g. wide ranges established on a multivariate basis).
- The manufacturing process principle is described.
- The equipment type is described.
- Process parameters are described (with target values or ranges) leading to a comprehensive description of the unit operation; for applications able to assign criticality to process parameters, both critical and non-critical parameters are described.
- There is a reduced list of process parameters remaining in the description compared to the "early development list" as the following has been taken into account:
  - Nature of the active substance (e.g. the active substance is chemically stable and thus there is no need to describe the environmental and product temperatures);
  - Degree of complexity of the dosage form (e.g. the proportion of active substance in the tablet formulation is high and thus there is no need to describe the pre mixing step in detail);
  - Degree of complexity of the process (e.g. the delumping of raw materials before processing is an optional step and thus there is 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 there is no need to describe the mixing parameters; the granulation solution addition is adequately summarized by the output "flow rate" thus there is no need to describe the liquid pressure and the pump speed).