Deconstructing the revised EMA guideline on **manufacture of the finished dosage form**

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Abstract
This article reviews the revised EMA guideline on manufacture of the finished dosage form (EMA/CHMP/QWP/245074/2015), which came into effect earlier this year. The new guideline is compared to both the original 1996 version and the draft guideline, published in 2015. Changes in scope and legal basis are outlined, as well as updated dossier requirements in terms of manufacture, manufacturer, batch formula, description of manufacturing process and controls, and control of critical steps and intermediates. Many stakeholders commented on the draft guideline during its consultation period; common themes from the consultation are gathered herein and discussed, together with related EMA feedback.

Introduction

The European Medicines Agency (EMA)'s "Manufacture of the Finished Dosage Form" draft guideline was issued for consultation on 9 July 2015 and adopted by the Committee for Medicinal Products for Human Use (CHMP) on 20 July 2017, coming into effect on 14 February 2018. According to the EMA: *"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 … are also taken into account."*

In this article, the text of the final guideline (EMA/CHMP/QWP/245074/2015)[1] is deconstructed by comparing it with that of the heavily outdated 1996 guideline[2] and the 2015 draft version,[3] and the main differences are summarised. Stakeholder comments received by the EMA during the associated consultation period[4] are also reviewed.

Scope of the updated guideline

The guideline's scope has been extended in comparison to the 1996 version. In addition to chemical and herbal products, its principles are now generally applicable to biological products, which were specifically excluded from the scope of the 1996 guideline. The guideline's principles can be applied to radiopharmaceuticals and chemical investigational medicinal products (IMPs), where relevant. Variations that affect the manufacturing process of authorised products now also fall under the scope of the new guideline.

Although the draft guideline specifically excluded advanced therapy medicinal products (ATMPs), the final adopted guideline does not. This indicates a further extension in scope; however, ATMPs have their own set of guidelines which need to be consulted before submission.

Legal basis

The guideline has been updated to refer to Directive 2001/83/EC Article 8.3(d).

Manufacture

As in the 1996 version, the guideline states that only product-specific aspects of manufacture need to be included in the marketing authorisation (MA) dossier, and general good manufacturing practice (GMP) elements should not be included. However, whereas previously the guideline focused on details that should be excluded, it now focuses on expected inclusions. To this end, an Annex has been published which explains the level of detail that should be submitted for both traditional and Quality by Design (QbD) applications. A specific manufacturing process step is used as an example, namely high shear granulation in production of a 200 mg tablet.

Manufacturer

Requirements in terms of manufacturer details are now more specific in comparison to the 1996 version, and have been further refined since the 2015 draft. Names, addresses and responsibilities of each manufacturer should be provided in Module 3, including those responsible for packaging and quality control, and contractors. Details should be given of all the individual sites involved, including those from the same company and those responsible for ongoing stability testing, if different from the manufacturing site. The EU site responsible for batch release to the EU market should also be specified.

Batch formula

Requirements have been tightened and the published guideline shows a general expectation of improved process knowledge and corresponding quality assurance, over both the original 1996 guideline and the draft revision published in 2015. This improved process knowledge ties in with ICH Q12 principles.[5]

The guideline continually asks for justification of aspects of the

Table 1: Expected level of detail in manufacturing process description.

Requirements
1. Comprehensive process description. 2. Process steps to be included in a sequential manner. 3. Batch size(s), operating principle and equipment type(s) for each unit operation. 4. Equipment working capacity to be stated where appropriate. 5. Process parameters to be stated together with target value or range. 6. Identification of critical process parameters (CPPs) as well as parameters important for manufacturing process consistency. 7. Description of non-critical process parameters, parameters whose impact on quality attributes cannot be ruled out and all parameters that are considered important for a given step in the manufacturing process or the output of the product. 8. Clear distinction between critical and supportive information, and justification for this categorisation.
Not acceptable
1. Reference to "suitable equipment". 2. Reference to "typical" set points (in regard of target values or ranges).

batch size and formula. Justification is expected if a range of batch sizes is used, if sub-batches are involved, and if commercial batch sizes for solid oral dosage forms are less than 100,000 units. Upper and lower quantity limits of each ingredient stated in the batch formula must also be justified, as well as overages and factorisation. Additionally, the expectation that reference is made to ingredient quality standards as in Module 3.2.P.1 (eg, magnesium stearate *Ph Eur*) is now formalised.

Reflecting updates in manufacturing since the original guideline was written, continuous manufacture and related requirements are also included in the updated guideline. In this case, although information about batch size in the traditional sense may not be relevant, information should be provided on how a batch is defined.

Description of manufacturing process and controls

The superseded guideline was published before the advent of the CTD dossier and Directive 2001/83/EC. Hence, the revised guideline incorporates current regulatory requirements and considers complex manufacturing processes and supply chains. Requirements have now been expanded significantly, and fall under the headers: general aspects; expected level of detail in the manufacturing process description; and technical adaptations in the manufacturing process.

- **General aspects.** The registered manufacturing process must be justified by development data submitted in Module 3.2.P.2 and any ranges considered wider than normal operating parameters are to be supported scientifically. The popular statement: *"Very detailed descriptions of the manufacturing process, apparatus and in-process controls should therefore be avoided"* precluding unnecessary applications for variations has been removed. Instead, a more detailed approach is now expected.

  Any specific environmental conditions relevant to the product should be stated. Hold times and duration of critical steps must be justified.

  The current guideline often makes reference to the extent of detail to be documented in the development module. These data should show that the manufacturing process and related controls guarantee product quality.
- **Expected level of detail in the manufacturing process description.** This is a new section in the current guideline. Starting off from the concept that relying exclusively on end-product testing is not sufficient to safeguard the consistent quality of the product, it follows that significant detail about the manufacturing process itself and respective process controls is necessary in the submission dossier. These requirements are laid out in Table 1.

  The Annex to the guideline provides clarification on the extent of detail that "could" be provided in the dossier.
- **Technical adaptations in the manufacturing process.** In consideration of complex supply chains, a new section has been introduced to outline the principles that come into play when multiple manufacturers and manufacturing sites are involved and technical adaptations may be necessary.

  Technical adaptations due to different equipment are acceptable as long as they are justified and it can be demonstrated that all steps of the manufacturing process consistently yield the same intermediate and finished products that comply with in-process controls and specifications.

  Where relevant, manufacturing processes with technical adaptations are to be shown in separate flow-charts within the same 3.2.P.3 section, differentiated for each manufacturing site if required. Alternative manufacturing processes that utilise different principles and may result in different in-process control or finished product quality are not acceptable.

Control of critical steps and intermediates

This is a new section in the guideline, as critical steps were previously mentioned only with respect to validation requirements. All critical steps and intermediates identified during manufacture of the finished product should now be listed in this section, including any in-process controls, test methods and acceptance criteria.

For complex control strategies, such as in continuous

The new guideline requires more detailed information to be included in Module 3.2.P.3 of the CTD, which is expected to result in the need for more variations

manufacturing, emphasis should be placed on the frequency of in-process controls, extent of release testing and how product release decisions are made. A description of how any unexpected deviations from the approved manufacturing process would be detected and managed is also expected.

In the development section, justification – based on experimental data – of steps that are being identified as critical or non-critical is expected.

The additional importance given to critical steps reflects GMP Annex 15 on Process Validation[6] (which came into force in October 2015) and ICH Q12, and once again shows a general expectation of improved process knowledge.

Following publication of EMA Q&A "Stability issues of pharmaceutical bulk products use in manufacture of the finished product"[7] in February 2012, industry was provided with clear guidance on regulatory requirements concerning the control of intermediates. This guidance has now been incorporated into the revised guideline.

A clarification has been provided to authors of CMC modules, namely: *"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"*, with the exception of specific types of products, eg, sterile or biological products.

While the requirements set out in GMP Annex 15 concerning transportation of intermediate product between manufacturing sites are to be adhered to, the guideline states that the impact of short or longer excursions outside of the original storage conditions should be discussed, supported by accelerated or real-time stability data. There was no mention of transportation in the 1996 guideline. The EMA Q&A (February 2012) and draft guideline (February 2015) refer to possible excursions in temperature supported by accelerated stability data. Therefore, the current guideline now additionally refers to the possible use of real-time stability data to support transportation storage conditions and any excursions outside of the original storage conditions.

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 and supported by bulk storage stability studies *or* by challenging maximum hold time in process validation studies.

Containers to be used for storage of bulk product and for transportation need to be justified and their materials of construction described. A control specification for primary bulk packaging is also required in Module 3.2.P.3.4, as had already been stipulated in the EMA Q&A.

Eliminated text

The "Special Items" section of the old guideline has been eliminated completely. This section covered Method of Sterilisation (the revised guideline simply cross-refers to a separate guideline for guidance on sterilisation); Re-processing of residual product; Removal of solvents or gases; Cleaning of primary packaging material; Sterilisation of primary packaging material; and Production areas. The section on Process Validation has likewise been eliminated and replaced by a cross-reference to the relevant guideline.

Overview of comments received on the draft guideline

Several interested parties commented to the EMA on the draft guideline during consultation, including individual companies as well as major industry organisations. There were a number of themes identifiable in the stakeholder comments and in the EMA's responses.

1 **Too much detail**

Stakeholders were concerned because the new guideline requires more detailed information to be included in Module 3.2.P.3 of the CTD, which is expected to result in more variations having to be filed eventually. They requested that the following text from the previous version of the guideline should be retained (or similar):

"It is in the interest of both the applicant and the regulatory authorities to avoid unnecessary applications for variations. Very detailed description of the manufacturing process, apparatus and in-process controls should therefore be avoided."

One stakeholder went as far as suggesting that the revised guideline not be published at all, because "*It will only lead to an increase of bureaucracy and will increase the manufacturing cost and the revenues of regulatory authorities – without any benefit for patients."*

The response from EMA was hard-hitting:

"…assessors throughout EU have observed a tendency for companies to provide less and less information in the manufacturing section to the point that there is little or nothing to assess. Therefore it is not the intention to go back to the statements of the previous guideline, as these statements have been misused in the past by some companies…The information about manufacturing process has to be submitted in sufficient detail to be assessed and understood…The aim is to ensure that important details, which can facilitate an appropriate assessment of the manufacture of the finished product, are included in the submission."

One can naturally identify with both sides in the discussion. It is undeniable that some dossiers simply do not provide enough information for a thorough assessment. Experienced regulatory professionals will know that the additional detail required by the guideline – from less vague language to transportation conditions – has been requested by assessors for many years, and all the guideline does is formalise the requirements. This levels the playing field, although it is certain that additional variations will be needed.

EMA did clarify that: "*The level of detail as given in the master batch record is not expected to be provided in the CTD Module 3"*, and also seems to be hinting that the guideline should be used intelligently: "*Prior knowledge of standard process* ***can help to set the process parameters in sufficient way without the need of further changes****. A type IA notification would in most cases be sufficient for such changes."*

2 **Conflict with ICH Q12**

Following on from the previous theme, stakeholders commented that the guideline conflicts with the intention of ICH Q12, which

is under development and is intended to streamline post-approval CMC changes. In its response, EMA claimed that: *"it is not expected that the new paradigm described in ICH Q12 will be compromised by this guidance"*.

In a discussion on critical versus non-critical process parameters (several stakeholders objected to inclusion of the latter in the manufacturing process description), the EMA commented: *"Expectations on handling of non-critical process parameters post-approval will not be covered by this guideline."* This leaves the door open for the ICH Q12 distinction between established conditions presumably requiring variations, and other non-critical parameters. According to the EMA, *"ICH Q12 will not be in contradiction with the proposed wording in this guideline… Expectations on post approval management will be covered by ICH Q12 guideline, which is currently under development."*

3 **Global alignment**

A couple of stakeholders commented that regulatory authorities globally should be aligned on their expectations on P.3.3, but the EMA replied firmly that "*this is EU guidance*".

4 **The Annex example**

Stakeholders objected to the Annex example of a manufacturing process description as being potentially unhelpful. They suggested that it be removed, because it provides too simplistic a differentiation between traditional and QbD approaches to product development, and also because the description needs must be so product-specific that an example is inappropriate. The EMA insisted that *"the general principles contained in the example should still apply"*.

The authors of this article are inclined to regard the Annex as useful.

5 **Site listing**

Objections were raised by several stakeholders on the need to include all sites involved in the manufacture of the product in Module 3. Specifically, stakeholders suggested that stability testing sites, batch control and release sites, packaging sites and storage facilities, especially contractors, are covered by GMP and should not be listed. However, the EMA insisted that all relevant sites should be listed both in Module 1 and Module 3.

6 **Applicability post-approval**

The scope of the guideline states: *"It also applies to variations for authorised products in cases where changes to the manufacturing process affecting the MA are proposed."* One stakeholder was concerned about the retrospective nature of this, especially in the case of older products and requested clarification, but the EMA pointed out that *"no action was taken as clarification on variations is not part of the text of this guideline"*.

7 **Overlap with GMP**

There were also some objections to information required by the new guideline as being more in the realm of GMP than marketing authorisation, eg, division pattern when bulk product is assembled into different presentations or packs; definition of sub-batches; control and sampling strategy; transportation of bulk product. Stakeholders protested that inclusion of this information in the dossier impacts on manufacturing and supply chain flexibility. However, the EMA explained that "*in some instances, the provision of GMP elements is needed in the CTD Module 3 to enable a better understanding of the company's position*".

New sections have been added to the revised manufacturing guideline describing the level of detail expected in the manufacturing process description, related technical adaptations, and control of critical steps and intermediates

Conclusion

The revised manufacturing guideline is a complete rewrite of the 1996 guideline, reflecting current assessment practices. A more detailed approach based on improved process knowledge is now expected. Requirements have been tightened in terms of manufacturer details and batch formula, and new sections have been added describing the level of detail expected in the manufacturing process description, related technical adaptations, and control of critical steps and intermediates.

The guideline is not without controversy. Its applicability post-approval is still unclear, and how it will ultimately tie in with ICH Q12 remains to be seen.

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