Brief analysis of the *Guideline on manufacture of finished dosage form* and its impact on the industry

Masterarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs, M.D.R.A.“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von
Silvia Londero

geboren in
Cividale del Friuli, Italien

Hamburg 2018

Erstgutachterin: Dr. Cornelia Nopitsch-Mai

Zweitgutachterin: Dr. Susanne Ding

La fortuna non esiste:
esiste il momento in cui il talento incontra l'opportunità.

(Lucio Anneo Seneca)

Table of Contents

List of abbreviations

CHMP	Committee on Human Medicinal Products
CMO	Contract Manufacturing Organisation
CP	Centralized Procedure
CQA	Critical Quality Attributes
CTD	Common Technical Document
CVMP	Committee on Veterinary Medicinal Products
DCP	Decentralized Procedure
EC	European Community
EMA	European Medical Agency
ICH	International Conference on Harmonisation
EU	European Union
GMP	Good Manufacturing Practice
IPC	In-Process Control
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
NfG	Note for Guidance
NP	National Procedure
NRA	National Regulatory Agency
NTA	Notice to Applicants
Q&A	Questions and Answers
QWP	Quality Working Party
RTRT	Real Time Release Testing

List of tables

1. General introduction

The Committee for Medicinal Product for Human use (CHMP) together with the single national regulatory authorities (NRAs) has drafted throughout the years a number of guidelines with the aim of helping the applicants to prepare the application for human medicines in a proper and harmonized way through all different types of procedures (CP, DCP/MRP, NP). In particular to suggest better ways to interpret and apply all the requirements in matters of quality, safety and efficacy, which are delineated in the EC directives [1].

The most difficult work is to maintain all these guidelines up-to-date and to maintain a cohesive stream of information which will not lead to any contradiction or ambiguity. In this context, a number of cyclical revisions are planned and done to each of these guidelines.
Moreover, the industry could require a re-examination of any guidance in case discrepancies or obsolete information are noticed.

In case one guideline is reviewed, each person who feels involved can comment the revised text through mail, stakeholders or public consultation. The Agency is then giving the public the possibility to ask for changes or explanation before a guideline is finalized or enters into force. These comments can be checked any time on the EMA Website, together with both versions of the guideline (before and after the comments)[1].

The “Note for Guidance on the Manufacture of Finished Dosage Form” [2] was first published in 1996 and a refreshment of the information was needed and demanded by both applicants and authorities. The work for updating this specific guideline, which provides clarification on the content of the module 3 of the MAA concerning the manufacturing process description, has lasted for four years. The first concept paper[3] was published in July 2013 and the final guideline [4] in August 2017 [1].

There are many changes that follow the implementation of this Guideline [4], due to the fact that more than ten years have passed between the first version and the

revision. Moreover, in these years the world of the manufacturing transformed itself completely.

The aim of this work is to give a brief analysis of the chapters of this Guideline [4] in respect to the relative MAA Dossier chapters and reflecting the latest experience from the applicant's point of view, analysing the reactions and the comments of the stakeholders or the industry and the probable impact on the daily work of the manufacturers and marketing authorisation holders (MAHs).

Since the area covered by this Guideline [4] is particularly broad, there are a number of aspects that could be taken into consideration, depending on the type of products (chemical, herbal or biosimilar) and the point of view (applicant or authority).
In this work the author has tried to summarize and report all possible perspectives, but sometimes the lack of experience in one or other field, could have led to imprecisions, for which comprehension is asked.

2. Executive summary

2.1 Extract from the guideline

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 [5] *are also taken into account.*

The guideline does not introduce new requirements on authorised medicinal product 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 and changes that may be required to enable the medicinal product to be manufactured and controlled by means of generally accepted scientific methods [4].

2.2 Analysis

As mentioned before, the common practice of the CHMP is to keep guidelines, notice to applicants (NTA) and questions and answers (Q&A) updated. This revised Guideline [4] is part of the reorganisation exercise to follow the CTD system and Annex I of Directive 2001/83/EC[6]. The aim is to substitute the “Note for Guidance on the Manufacture of Finished Dosage Form” [2] published in 1996, which has become obsolete and is not reflecting the state of art any longer [1].

Due to the constant evolution of the formulations and the manufacturing techniques, it has become more difficult for the European Medicines Agency (EMA) and all other national regulatory agencies (NRAs) to assess the documentation provided from the applicants and to provide a detailed guidance on how to present these data, in order

to find the balance between a detailed description of the method and to leave a decent range to be followed in routine manufacturing [7].
Furthermore, the extension of the number of patent registrations in different countries and the difference of the costs for the same manufacturing around the world, have opened a scenario of complex supply chains and movement of manufacture-intermediates on a regular basis.

Although most of the new or revised guidelines apply only to new products, after a marketing authorisation has been granted, the marketing authorisation holder (MAH) shall, in respect of the methods of manufacture and control provided described in the regulations, 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. Those changes shall be subject to the approval of the competent authority of the Member State involved [6].

2.3 Impact on the industry

The industry have appreciated the efforts of the Agency to update the former Note for Guidance[2] to the state of the art and has participated actively in its correction, even though the request of details and the subsequent constant need to file variation has generally been not easily accepted [7].

The deletion of the phrase previously included in the Note for Guidance [2]:

> *"It is in the interested of both the applicant and the regulatory authorities to avoid unnecessary applications for variations. Very detailed descriptions of the manufacturing process, apparatus and in process controls should therefore be avoided."* [2]

has been read as a loss of pragmatism from the Agency. On the other hand, the assessors throughout Europe have noticed a tendency from the applicants to misuse this and to provide less and less detail in the dossier. Therefore, the EMA has solidly decided to maintain its position and to request a description including important details, which can facilitate an appropriate assessment of the manufacture. The EMA insists that such many more variations than usual will not be triggered from the

implementation of this Guideline [4] due to the fact that those are simply based on the common practice [7].

Despite of this, it will surely be a challenge for the industry to discuss with the national authorities, more than with the EMA, whether a detail is considered necessary or surplus to an assessment.

3. Introduction (background) and scope

3.1 Extract from the guideline

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.

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.

(...) 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)[8], *should not be included* [4].

3.2 Analysis

The aim of this Guideline [4] is therefore to explain what needs to be included in the chapters and in which detail, following the CTD structure.

It is also underlined how it is important to see this Guideline [4] as a link between ICH Q8 [5] approved since 2006 (Development - 3.2.P.2) and the validation guideline [9], more recent - 2014, (Validation - 3.2.P.3.5) in order to have a more cohesive dossier.

The applicability of this Guideline [4] is wider than the previous Note for Guidance [2]: further than to chemical and herbal medicinal products for human use, this applies also to variations to the process, biologicals, radiopharmaceuticals and chemical investigational medicinal products. This reflects the state of the art, where manufacturing biologicals has become as widespread as manufacturing herbal or chemical medicinal products.

Meanwhile, the CHMP, CVMP and QWP have been working on a separate guideline on the sterilisation [10]; hence no mention of this practice has been included in this Guideline [4] [7].

All aspects belonging to GMP have to be avoided as per previous practice; nevertheless the Agency is of the opinion that the provision of certain GMP elements is needed to enable a better understanding of the common manufacturing practice of the manufacturer [7].

Annex 15 to the Eudralex volume 4 [11] remains the main guidance on qualification and validation, describing what is to be understood as Good Manufacturing Practice.

3.3 Impact on the industry

Since the level of details required has increased, it is understandable that differences between chemical/herbal and biological/radiopharmaceutical medicinal products are no longer an issue, and hence both categories fall into one guideline.

This could lead to a better approach to the dossier from companies which are dealing with different types of medicinal products. Nevertheless the opinion of most stakeholders is that the Guideline [4] is too extensive to be helpful while writing the dossier, requiring specific guidelines for each type of medicinal product.

On the other hand knowing the variety of the medicinal products for which a MAA is made every day, it is not possible to describe each single case in detail. Hence the Agency had no other chance than to collect the manufacture of all medicinal product under a single guideline.

4. Legal basis

4.1 Extract from the guideline

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].

4.2 Analysis

When the Note for Guidance [2] was published the legal basis were the Directives 65/65/EEC [12] and 91/507/EEC [13]; these have been replaced after the founding of the European Union by the Directive 2001/83/EC [6] and various amendments took place over the years.

Annex I [6] describes the minimum information that has to be included in the MA dossier and reflects what was already covered by the previous Directive.

4.3 Impact on the industry

In this chapter no more changes have been included, since the three directives[6][12][13] are mirroring one another in this point.

Attention should be brought to the legal difference between a directive or a regulation and a guideline. The first two are part of the mandatory law, and have to be followed. Guidelines and communications on the other hand are part of the non-binding law, they suggest how to behave in a certain position and any deviation sufficiently justified should be accepted from the legal bodies [14].

This implies that the applicants have to include *per se* only the information listed in the Annex I of the Directive [6] and they can avoid the inclusion of further information if they are able to justify the absence. Still this can apply only if the applicant has plenty of knowledge about of his manufacturing process, and this is exactly what the Agency is demanding.

5. Manufacturer(s) / 3.2.P.3.1

5.1 Extract from the guideline

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].

5.2 Analysis

This passage is taken exactly from the Annex I to the Directive [6], except for the details of the EU release. The Agency requests the listing of all involved sites in module 3 as described in module 1.

5.3 Impact on the industry

As mentioned before the supply chains have become increasingly complex, hence the inclusion in this chapter of information previously only stated in the annex 5.8 to the application form (module 1) has brought a lot of comments from the industry [7].

Nowadays it is common practice to contract an external laboratory for certain analysis, and it is common as well that this external laboratory is contracting another external laboratory for further analysis.
Unfortunately, this scenario does not depend on the will of the applicant and can change quite often, as per single commercial or technical decisions. These external laboratories are included in the manufacturing licence of the main one and hence, can all be used, thus should be all listed in 3.2.P.3.1 as per Guideline [4]. This situation will lead to a large number of administrative changes that will influence the dossier, without having any impact on the quality of the medicinal product.

Now, a lot of national agencies have included annual fees to cover administrative changes, but the most of them still require fees for each variation, not excluding the workload that these, even though small, variations are generating in the companies and regulatory bodies as well.

Furthermore, there are a big number of companies which are offering regulatory service, mostly to generic companies, submitting parallel procedures with different supply chain, especially regarding packaging, control and release; and are forced to maintain a common dossier (modules 2-5) to speed up and simplify the assessment.

Despite all the comments and the voices against this, the Agency has been quite clear on this and has rejected all the comments on this part, explaining that module 3.2.P.3.1 should be in line with the information in module 1 [7].

Still the recent experiences have shown that it depends on the authorities involved in how much detail the information in 3.2.P.3.1 should be given. Some of the authorities will consider as sufficient the inclusion of the main site in the dossier and in the application form; leaving the information on the contract laboratories to the annexes of the manufacturing licences of the main ones. These are in fact listed and can be consulted in the Eudra GMP database [15], and hence always updated.

6. Batch formula / 3.2.P.3.2

6.1 Extract from the guideline

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 [9].

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) [9].

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].

6.2 Analysis

This section has been extensively rewritten. It has been included the possibility, differently from the previous Note for Guidance [2], to define the batch size as a range, clarifying that batch formulae should be presented for at least the highest and lowest batch sizes.
A proper justification has to be given stating that the range is not impacting the critical quality attributes, hence that the quality of the product remains the same independently of the batch size.

This is underlined by referring to the validation guideline [9]:

> *"Where ranges of batch sizes are proposed, it should be justified that variations in batch size would not adversely alter the CQAs of the finished product. It is envisaged that those parameters listed in the process validation scheme will need to be re-validated once further scale-up is proposed post-authorisation*

unless the process has been proven to be scale independent or continuous process verification is employed." [9]

In case of the traditional validation approach, ranges are allowed if proper validation is conducted for each scaling up.

The batch size has to be defined based on the compatibility of the commercial equipment and be representative in order to demonstrate the knowledge of the process. The example of 100,000 units as per standard commercial batches has been linked with the only detailed definition of batch size in the validation guideline [9].

"It should be noted that pilot batch size should correspond to at least 10% of the production scale batch (i.e. such that the multiplication factor for the scale-up does not exceed 10.) For solid oral dosage forms this size should generally be 10% of the maximum production scale or 100,000 whichever is the greater. Where the intended batch size is less than 100,000 units, the predictive value of the pilot batches may be limited and a justified approach should be followed. For other dosage forms the pilot batch size should be justified taking into account risk of the patient of failure of the dosage form." [9]

Contrary to the common understanding on this topic, it is then acceptable to use smaller batches as pilot batches if there is no aim on scale-up, or the equipment or the market are limited. That Agency underlined also that *"with proper justification, other products (than orphan drugs n.d.r) might also manufactured at a smaller scale"* [7].
In any case the formulae and numbers of sub-batches should be stated and justified. Due to the increase of non-standard manufacturing process, further definitions of batch size (such as quantity of product/time) are allowed and need to be clearly stated.

The old Guidance [2] was quite lenient with regard to actual quantities of ingredients compared to nominal quantities, whereas the current Guideline [4] recommends that upper and lower acceptance limits may be proposed only when justified.

If the overage regards the drug substance, this should be also explained in detail in 3.2.P.2 section 2.2.2 overages. Nevertheless a use of an overage of drug substance to compensate degradation during manufacturing or shelf life remains discouraged [5].

Further on in this chapter should be stated the final formula, the one that will be used in the commercial batches. And change during the development and/or after the production of exhibit batches should be justified and cross linked in 3.2.P.2 section 2.2.1 formulation development [5].

6.3 Impact on the industry

Surely it has been appreciated the clear permit to use ranges, which has become common practice but never allowed as openly as in this Guideline [4].
On the other hand the passage including the division pattern has been debated, since it should be a matter of GMP. The Agency seemed quite firm on announcing that basic information on the pattern division is important to understand the manufacturing strategy [7].

The biggest concerns are on the division into different packages (e.g. 30 ml or 60 ml bottle) and the division of common blends in different strengths. These decisions are not made during development, and if they are there could be always a change to fulfil the current market demand.
The stakeholders are afraid that such detailed information in the dossier can lead to unneeded variations, which can be also turn out more difficult than expected. Not to consider, as for other such situations, the workload and the costs that are arising in both companies and authorities [7].

The wording on the continuous manufacturing process has been indeed triggered by the comments of the industry hence is not bringing any observation [7].

From a practical point of view the structure and content of this module remains unchanged. Thus this chapter of the Guideline [4] will not lead to many changes.

7. Description of manufacturing process and process controls / 3.2.P.3.3

7.1 General aspects

7.1.1 Extract from the guideline

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 [9]*. 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* [16] [17].

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)[18] *is proposed, a design space* [5] *is claimed, a continuous manufacture or a standard manufacture is performed* [4].

7.1.2 Analysis

Following the progress of the manufacturing techniques this dossier section has become more important and hence the Guideline [4] is more exhaustive in this chapter. The information in 3.2.P.3.3 should be a directly cross-linked with 3.2.P.2.3, as the manufacturing process chosen is a direct consequence of the development of the same. Hence more details have to be included in the development section, whereas only the conclusions should be listed in the actual description [5].

The structure of this section remains a full text description followed by a flow chart for an immediate understanding of the process. In process controls (IPCs) should be identified, but their specification and their description have to be included in section 3.2.P.3.4.

As stated in the guideline for the process validation of finished products [9], standard processes could be validated only at commercial size and validation reports are not necessary by the time of submission. Hence it could be noticed during the forthcoming validation that some CQAs, IPCs or process parameters have been defined wrongly in the initial submission, and then a variation is required.
Again in the revised Guideline [4] the importance and in certain cases the necessity of the variations is underlined, differently from the older one [2].

The requirements for the particular variations should be taken from the variation guidelines [16] [17].
It is implicit then that non-standard processes need to be validated and the validation reports have to be included in 3.2.P.3.5, to let the authorities understand the process best [9].

There could be, depending on the product, extra environmental conditions that should be followed during the process in order to assure the good quality of the same. If this is the case then these should be listed and justified. Accordingly, these conditions have to be monitored and reported following GMP [8].
The same concept applies for the duration of critical steps and holding times, if the nature of the product requires it, for example a sterile product, detailed information is reported in the draft sterilisation guideline [10].

As underlined before, it is really important for the authorities to understand that the applicant has a deep knowledge of the process and the quality of the finished product. The strategies to control and guarantee the quality of the product or intermediates should be discussed again in detail in 3.2.P.2 and the results included in 3.2.P.3.3. It has to be ensured that the quality of the drug product is maintained during the lifecycle and is corresponding to the quality of the drug product that has been used in the clinical studies. An appropriate level of detail and strategies used to control this product have to be chosen in respect of the type of development (design space, empirical approach...), type of process (standard, continuous, non-standard...) and type of knowledge (first product with this process, tenth product with the same approach...) [19] [20].
The Guideline [4] is referring here to different aspects of the development as described in ICH Q8 [5], to different types of release testing such as real time release testing [18].

The applicant should choose the proper control strategy and release strategy depending on the product and manufacturing process used. This information should be discussed in 3.2.P.2 and reported in 3.2.P.3.3 as final conclusions.

7.1.3 Impact on the industry

The stakeholders have participated actively on the correction of this chapter, and the changes from the draft to the final version are showing this. Nevertheless the further recall to the necessity of the variations is still not accepted by the industry. The reasons are the ones already listed above. Again the Agency is not doing any step back and remains of the idea that critical and non-critical parameters should be stated in this chapter and any deviation during future validation should be reported [7].

A further common opinion from the industry is that accordingly to what is written in the relative guidelines[19] [20] the quality control strategies and management is a matter of GMP. Here the Agency is underlining the importance of the inclusion of the general information on these topics into the CTD Dossier. The connection between the process and the quality management should be acknowledged [7].

In daily practice, nevertheless the information on the chapter was not that exhaustive in the previous Note for Guidance [2], there will not be a major difference in module 3.2.P.3.3 regarding the general content.

7.2 Expected level of detail in the manufacturing description

7.2.1 Extract from the guideline

Although it is expected that the process description is considered in relation to the control strategy [5], *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 [4].

7.2.2 Analysis

Even though the ICH Q8 [5] clearly allows a rather vague description of the development of the manufacturing process in 3.2.P.2, to enable flexibility for its improvement, focusing on the control of critical attributes or process end points more than on the process itself, in this chapter (3.2.P.3.3) the final process needs to be described in detail. The reason is that the quality of a product is not depending only on the testing of the end product.

The process has to be described in a comprehensive way; the process' steps have to be mentioned in sequence including the equipment characteristics (such as batch size or capacity, operating principle and type) for each unit operation.
The process parameters and the target values or ranges should have also to be included in sufficient detail.
It is no more possible to include imprecise references to "suitable equipment" or "typical set point", nonetheless the inclusion of serial number or model is not required.
The focus should be set on the CPPs, but the inclusion of information on the non-critical parameters is deemed necessary in case these are important for the consistency of the manufacturing process. Nevertheless, the information which is purely supportive should better be identified and explained.
A well described manufacturing process is relevant for the understanding of the assessor.

The level of detail that is applicable to the narration of the manufacturing process remains independent from the type of development that has been chosen, whether traditional or quality by design. If the process is continuous, the same information should be found in the description.

7.2.3 Impact on the industry

The Agency dedicates a whole chapter on the expected level of detail that should be used to describe the manufacturing process. This is clearly appreciated by the stakeholders, who have helped to rewrite it, including a lot of comments and change proposals. Anyway the general opinion is that the EMA is still focusing too deeply into details which will lead to unwanted variations. This will lead to more discussions with the single NRAs during future MAAs [7].

It is clearly no more allowed to reference to "suitable equipment" or "typical set point"; but still the inclusion of serial number or model is not required, differently from the requirements from more stringent countries such as USA or Canada [21][22].

In a context where it is not necessary to have performed the validation to submit a MAA, the expected level of detail could lead to the need of variation, after performing it. On the other hand, the Agency has already clarified the importance of the knowledge of the process and the product for which the authorisation is under review. Hence a suitable description of the parameters can be included even not having performed the process validation and it should help the review of the process from the Assessors.

In any case unnecessary details should be avoided, such as SOPs or pure GMP issues. Nonetheless the way how the deviations from the standard process will be investigated and addressed should be understandable from module 3 of the dossier, fulfilling the ICH Q9 and Q10 [19][20]. The Guideline [4] has been also adapted so that the information included in the dossier will be in line with the ICH Q12 [23] on the CPP and non-critical parameters [7].

Again the message of the Agency is that there will be no more differences between the different types of medicinal products and the type of development regarding the content of the dossier. The choice of a unified line of guidance can be read in all new guidelines.

7.3 Example (Annex)

7.3.1 Extract from the guideline

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

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.

Table 1 - Process parameters settings (minimal/traditional 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* *Granulation solution amount*[#] *Impeller speed* *Chopper speed* *Time*	*9 kg/min* *15% w/w* *90 rpm* *0* *3 minutes (2-4 minutes)*
6/ Wet massing	*Impeller speed* *Chopper speed* *Time*	*170 rpm* *2000 rpm* *5 minutes (4-6 minutes)*
7/ Wet massing 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.*

Table 2 - 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* *Granulation solution amount*[#] *Impeller speed* *Chopper speed* *Time*	***Non CPP*** ***CPP*** ***Non CPP*** ***N/A*** ***Non CPP***	***5-15** kg/min* ***12-18**% w/w* ***80-110** rpm* *0* *2-4 minutes*
6/ Wet massing	*Impeller speed* *Chopper speed* *Time*	***CPP*** ***CPP*** ***CPP***	***150-190** rpm* ***1800-2500** rpm* ***3-7** minutes*
7/ Wet massing screening	*Screen size*	***Non CPP***	***0.595 – 1.41** 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.*
**Ranges established on the basis of multivariate evaluation.*

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)* [4].

7.3.2 Analysis

This Annex is trying to give the applicants an example of how the module 3.2.P.3.3 should be written, to translate all the words into something more tangible and reliable in case of doubts. It describes a quite standard process, such as wet granulation, probably to achieve more understanding, in a quite detailed way.

The first step that an applicant should do is to list all involved parameters into the development and to select from these the ones which should be closely monitored or controlled after the experience gained in the development.

The narrative description (which will be the same despite of the type of development) should classify the steps of the process including the type of equipment used independently from the process parameters settings. These will be then listed in a separate table including the information on the step, the parameter involved and the target value or range.

In this tabular description the different type of approach can be read, meaning that a “traditional approach” will list fixed target values and smaller ranges, whereas an “enhanced approach” could use wider ranges and provide more information on the criticality of the parameters themselves, due to deeper mathematical and empirical analyses during the development itself. These wider ranges will later avoid a lot of variations and will lead to fewer quality issues during the control of the manufacturing.

Of course the level of detail will depend on the number of active substances in the product, on the degree of complexity of the dosage form and the degree of complexity of the process.

7.3.3 Impact on the industry

The majority of the stakeholders are not approving the inclusion of an example in the Guideline since the majority of the NRAs will probably insist on the example as the only way to include the description of the manufacturing process. This has not changed the opinion of the Agency and hence a certain level of detail has been included in this Annex.

Moreover there was a deep work from the industry to align each detail of this example to what was written previously in this and other Guidelines. This cooperation has been appreciated from the Agency that has rewritten the Annex accordingly [7].

The expectation of the industry is that the NRAs will understand the scope of an example and will not demand the same exact structure to the applicant concerning this chapter.

7.4 Technical adaptations in the manufacturing process

7.4.1 Extract from the guideline

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].

7.4.2 Analysis

In this complete new chapter it is underlined the new aspect of the manufacturing: the use of different equipment or different manufacturing sites for the same process steps. The main important requirement is that, regardless of the differences between the manufacturers and equipment size and brand, the same essential process should be used for a certain medicinal product. Hence the use of alternative processes will lead to different products with different quality and quality controls.

Nonetheless a certain space in technical adaptation is allowed when different manufacturers or equipment are involved.

All adaptations should be clearly described and justified, and it should be demonstrated that these will not lead to any difference in the product and its quality.
The IPCs and the final specifications should be applicable and the ranges and limits fulfilled.

Sometimes there could be a need of separate flow charts in order to let the assessors understand the differences and the adaptation in each single step and manufacturer.

The Guideline [4] is then including an example of which adaptations could be necessary, such as the preparation of the same liquid dosage form could be done in different equipment types with different parameters or slightly different tools.

As well for solid dosage forms different equipment can be used for the same granulation or coating method maintaining the IPCs and the results as described and developed.

7.4.3 Impact on the industry

This chapter has been deeply changed from the draft to the final version, since some incongruences and ambiguities have been commented from the stakeholders. However the inclusion of the possibility to technically adapt the equipment in case of different manufacturers has been awaited from the industry and positively welcomed.

Any information on future variations has been intentionally avoided from the Agency, since it is not in the scope of this Guideline [4].
The industry tried to exclude some details to allow more space in the production, the Agency underlines how a product is being defined by its unique process and hence different processes must result in different products, hence be described in different dossiers.

This complete new approach to this dossier module required by the authorities will impact the industry from different angles.
First of all, there are a lot of companies using different sites for the manufacture of the same product, and all these are listed in the dossier (3.2.P.3.1).
According to the guideline for the process validation of finished products [9] it is not necessary to perform the validation prior to submission, hence the information requested in detail in 3.2.P.3.3 could not be available by the time in which the dossier is written and submitted.
Hence, once the validation will be performed, the applicant/MAH will be forced to submit a variation, even though the IPCs and their parameters have not changed, just because the information on the new contract manufacturing organisation (CMO) has to be included in this module as technical adaptation.
It is in fact improbable that the equipment will remain identical, even if the process is not impacted.

Furthermore the later change or inclusion of a new manufacturing site will lead to a major change in the dossier; hence the variations will be more difficult to prepare and to assess, likely leading to longer clock stops or delays.

8. Controls of critical steps and intermediates / 3.2.P.3.4

8.1 Controls of critical steps

8.1.1 Extract from the guideline

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 [4].

8.1.2 Analysis

In this dossier section all the critical steps and parameters, which have been identified before in the module section 3.2.P.3.3, should be listed together with the IPCs, test methods and acceptance criteria.

In case of complex processes complex control strategies should be used [19][20], and the description in this section should be done accordingly. For example the frequencies of the IPCs and the information on how the product will be released should be listed in detail.
Moreover the strategy to control and detect the unexpected deviations should be included in this section as well.

In particular it should be clear that the criticality of quality attributes is not depending only on the fact that the parameter is within a range. A step could be critical even though it is controlled: the risk is reduced by including ranges and information on CQA but this is not sufficient to eliminate it, hence monitoring should be performed[19][20].

The criticality of the steps should be justified and linked to experimental data in the development part, if applicable.

8.1.3 Impact on the industry

Even though this chapter was absent in the previous Note for Guidance[2], the inclusion of the above mentioned information has become common practice in the last years as described in the Notice to Applicants Volume 2B [24]. Thus the impact on the future MAAs will be moderate.

Anyway the stakeholders have commented this chapter as well trying to differentiate the purely GMP information from the regulatory one. This has not been accepted by the Agency, insisting on the understanding of the process and its controls [7].

8.2 Storage of intermediate and bulk products

8.2.1 Extract from the guideline

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[25]. *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].

8.2.2 Analysis

Intermediate product and bulk product differ from the type of processes they should undergo: the bulk is missing only the packaging process whereas the intermediate will undergo other processes such as further granulation, coating and others. The same definitions are taken from the WHO Annex 4[26] which is giving guidance to the industry and the inspectors in matter of GMP.

A manufacturing process is involving different intermediates that will be processed to become bulk and then be packed in the final packaging.

The Guideline [4] is openly allowing storage of both intermediates and bulk in suitable containers and transport of which if necessary. Sometimes some tests will be performed before continuing the process.

All this information is purely GMP matter and should not be included in the MAA dossier. Nevertheless there are some particular products (e.g. sterile or biological products) for which some data should be presented in the dossier to allow the assessor to guarantee for the quality of the product.

If this is the case, the storage conditions (temperature, humidity and other environmental conditions) should be included in necessary detail depending on the type and nature of bulk product.

The maximum holding time and or the maximum process time has to be stated and clearly justified including relevant data on support.

As per standard understanding a “prolonged storage” is intended as more than 30 days for solid oral dosage forms and 24 hours for sterile products. All further claiming should be justified by supportive data on at least two pilot scale batches. Different conditions from ICH guideline can be used but clearly stated.

The shelf life should be then calculated accordingly to the relevant note for guidance [25]. Which is stating that, the expiration date of a batch should be calculated from the

release date, this date should not exceed 30 days from the manufacturing date. If the release is happening after (e.g. in case of bulk storage longer than 30 days) then the production date will be considered as starting time point, in particular the date of the first manufacturing step.
Any deviations from this guidance [25] should be justified by including supportive data.

The transportation of both bulk and intermediate is described in the GMP Annex 15[11] and in the question and answers on quality part 2 [27] and the same should be followed. Among other GMP requirements, this Annex is stating how to transport under good practice: the transport should follow the conditions approved during the MAA, the transportation routes should be defined even though challenged by variable factors, a risk assessment should be performed in case of any deviation is occurring and the transport should be monitored constantly [11].

Even though this information is purely GMP matter and there is no need to include it in the dossier, the impact of the temperature and humidity excursions out of the chosen storage conditions should be supported by accelerated data in 3.2.P.3.4 together with the justification and specification of the suitability of the container.

8.2.3 Impact on the industry

The information commented here above has been revised in detail from the industry in order to keep it in line with all the previous guidelines [7].

From the general point of view, no big changes are expected by the introduction of this chapter in the revised Guideline [4] since these GMP matters were already introduced and known.

The only aspect which will lead to some challenges during the initial switch to the revised Guideline [4] will be the now-clear requirement of "*at least two batches*" for the hold-time stability studies. The previous related guideline (WHO Annex 4 "General guidance on hold-time studies") [26] was stating that "*one or more batches*" could be used to define the hold-time.

Hence the common practice up to now was to refer to only one batch in case of stable products.

Nevertheless, since the Guideline [4] allows justification, an explanation could be given, and comprehension from the authorities is expected on this topic.

9. Process validation and/or evaluation / 3.2.P.3.5

9.1 Extract from the guideline

Description, documentation, and results of the validation and/or evaluation studies should be provided in this section. For more details see Process Validation guideline[9][4].

9.2 Analysis

Contrary to the previous Guidance [2] the Agency has decided to eliminate every reference to the validation, since in the last decades a specific Guideline has been written and has come into force in 2016.

9.3 Impact on the industry

Some stakeholders have required a brief description of the contents regarding this chapter in this Guideline [4] but the authority has declined firmly this proposal, in order to avoid any redundancy [7].

10. Eliminated Text

In the previous Note for Guidance [2] there was a further section named “Special Items” that has been deleted in the new version [4].
In particular the information on method of sterilisation, re-processing of residual product, removal of solvents or gases, cleaning of primary packaging material, sterilisation of primary packaging material and production areas is no longer to be found in this Guideline [4].

As stated in the scope of the current Guideline [4], due to the new guideline on sterilisation [10] each reference has been deleted.

The Note for Guidance [2] was stating that the re-processing of residual product, cleaning of primary packaging and details on production area are a matter of GMP and hence are covered by the phrase in the initial chapters of this Guideline [4]:

> “*Only product specific aspects of manufacture need to be described and included in the MA dossier; general elements of Good Manufacturing Practice (GMP), should not be included.”* [4]

Further on the use of solvent or gases should be stated in the batch formula and justified in the development part of the dossier.
Hence each extra mention in this Guideline [4] would be redundant.

This is not impacting the applicants, since all these aspects are covered already by other guidelines and detailed information can be found if needed.

11. Conclusion

The importance of this Guideline [4] and its update was known to both applicants and authorities, and both have worked together in order to achieve a cohesive, coherent and detailed information on how to write this dossier section describing the manufacture of the finished product.

Of course both parties have tried to write and rewrite each section in the way that could help and facilitate their daily work, but in some cases compromises and mandatory law should apply.

The result of this cooperation is a Guideline [4] which is outlining in greater detail than the previous one [2], what should and should not be included in the MAA dossier.

This will help the applicants in their writing but also eliminate some freedom of interpretation especially when stricter authorities will review the dossier.

The Agency's aim remains to force the manufacturers, through the high demand of details and justifications, to know their manufacturing processes in deep detail and to understand how to avoid all the accidents that can happen.
The longer goal is however probably to reach a point at which all processes will be enhanced processes and the maintenance actions will be reduced by the ranges included in the initial application and by the quality risk management and pharmaceutical quality system [19][20].

Initially there will be surely some problems adapting the current way of thinking to the one underlined by this Guideline [4], however the author is of the opinion that both applicants and authorities will adapt and will be able in a couple of years to reach a better harmonization in the dossier during initial application and lifecycle management.

Nevertheless, following the constant development and changes of the science and the manufacturing techniques, there will be the need in a near future of a further adaptation.

References

1. EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb [accessed on 15.06.2018]
2. “Note for Guidance on the Manufacture of Finished Dosage Form” – CPMP/QWP/486/95
3. “Concept paper on the need for revision of the note for guidance on manufacture of the finished dosage form” - EMA/CHMP/QWP/324350/2013
4. “Guideline on manufacture of the finished dosage form” - EMA/CHMP/QWP/245074/2015
5. “ICH guideline Q8 (R2) on pharmaceutical development” - EMA/CHMP/ICH/167068/2004
6. Directive 200/83/EC as amended
7. “Overview of comments received on 'Draft Guideline on manufacture of the finished dosage form'” - EMA/CHMP/QWP/104223/2016
8. Eudralex volume 4 (GMP Guidelines)
9. “Guideline on process validation for finished products - information and data to be provided in regulatory submissions” - EMA/CHMP/CVMP/QWP/BWP/70278/2012 -Rev1,Corr.1
10. “Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container – Draft” - EMA/CHMP/CVMP/QWP/BWP/850374/2015
11. Annex 15 - Eudralex volume 4 (Qualification and validation)
12. Directive 65/65/EEC
13. Directive 91/507/EEC
14. EC website https://europa.eu/european-union/eu-law/legal-acts_en [accessed on 15.06.2018]
15. EudraGMP website http://eudragmdp.ema.europa.eu/inspections/logonGeneralPublic.do [accessed on 15.06.2018]

16. 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
17. 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
18. “Guideline on Real time release testing” - EMA/CHMP/QWP/811210/2009-Rev1
19. “ICH guideline Q9 on quality risk management” - EMA/CHMP/ICH/24235/2006
20. “ICH Q10 (Pharmaceutical quality system).” - EMA/CHMP/ICH/214732/2007
21. “FDA Guidance for Industry – M4Q: the CTD – Quality”
22. GUIDANCE DOCUMENT - Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)
23. “ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management – Draft” - EMA/CHMP/ICH/804273/2017
24. Notice to Applicants Volume 2B - Medicinal products for human use
25. “Note for guidance on start of shelf-life of the finished dosage form” – CPMP/QWP/072/96
26. WHO Annex 4 “General guidance on hold-time studies”
27. Quality of medicines questions and answers: Part 2 – EMA website http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp&mid=WC0b01ac058002c2b0 [accessed on 12.07.2018]

Acknowledgments

My warmest thanks are for Frau Nopitsch-Mai who has helped me in the compilation and correction of this master thesis. A special thank is going to Johann too, who has done the grammar check thanks to his mother tongue.

I deeply thank Frau Röcher, Frau Fahnenstich and Frau Eibl for having supported me during the whole master and for all the help with the German burocracy of the university (which is quite similar to the Italian one from the amount of papers!). And then how can I forget all the persons I met and known at the courses? Even though some friendships are lasting the time of the need, it was a pleasure and it helped me grow.

In Italy we are usually thanking at the end of a path, all persons who have made it possible, willing or not, for us to reach this exact point.

That's why I feel the need to list here Maike, for giving me a chance, the chance. And of course all the colleagues that have raised me, teaching me all the details of this particular job: Florian, Gaby, Judith, Celine, Susanne, Meike and all the others. And then all the new ones who are fighting with me day by day, the RA Angels: Ina (also for the correction of the homework), Florentina, Inga, Christin and Esther. Furthermore all that colleagues that understand my being Italian as strength instead of a weakness, and appreciate my daily effort.

Ringraziamenti

I miei più sentiti ringraziamenti vanno a Frau Nopitsch-Mai per avermi aiutata nella stesura e nella correzione di questo lavoro di tesi. Un grazie particolare anche a Johann per la correzione linguistica, grazie alla sua madrelingua.

Poi un grazie profondo va anche a Frau Röcher, Frau Fahnenstich e Frau Eibl per l'appoggio durante il master e per tutta la burocrazia universitaria (in questo la Germania non è molto diversa dall'Italia!).
E come dimenticare le persone che ho conosciuto durante questo master? Per quanto certe amicizie siano circostanziali, è stato un piacere e mi ha fatto crescere.

Di solito da noi si usa ringraziare, alla chiusura di un percorso come questo, anche tutte le persone che in un modo o nell'altro hanno fatto in modo che si arrivasse fino a questo punto.

Per questo mi sento in dovere di citare Maike per avermi dato una chance, la chance. Poi certamente i miei colleghi che mi hanno cresciuta, insegnandomi i risvolti più nascosti di questo particolare settore lavorativo: Florian, Gaby, Judith, Celine, Susanne, Meike e tutti gli altri. E poi le nuove leve che mi appoggiano fianco a fianco tutti i giorni, le RA Angels: Ina (anche per le correzioni dei compiti a casa), Florentina, Inga, Christin ed Esther. E anche tutti quei colleghi e quelle colleghe che vedono la mia italianità come un punto di forza invece che una debolezza, e apprezzano lo sforzo quotidiano.

These years in Hamburg wouldn't have been the same without Marta, Ana, Isa and all the people that appeared and disappeared during all the weekends spent between the Comfort Zone and Mio Gelato trying to survive, integrate and remain unique. Thanks to all the Italians I met in the same occasions, adventures companions. Thanks also to Luisa to have helped me integrating in her "Heimat".

If I reach this point, it is also thanks to my break in Ulm, to Ulli, Paula and Eva. To their support and cheering up, besides the fact that they gave me a further house to miss. Thanks to my multi-culti Ulmer Family: Srihari, Erica, Jennia, Noemi, Marion, Rodrigo, Matheus and Rebecca, to the awesome nights out with them. To the Latinos: Kleber, Javi and Emmanuel and those ignorant nights with deep talks. And to that someone (Joe), who remembered me on a Monday evening in MoBar, that when nothing is sure, everything is possible, even to find a real job.

And then thanks to all the people who have always been there and will always be. And to the ones who were there and got lost, but therefore not less important.
To Casa K. (in the persons of Aly and Sara), to the University ones (Fabio, Cesare, Vale, Mary..) and to Trieste generally speaking (Mario).
To Isa, Stella and Robi.
To my roots in Friuli, which have always been too tight for me but with a huge place in my heart: Noni, Pince, Chiara, Sara, Linas, Lele, Trac, Slobbe, Greg, Dani, Giorgino, Tuiter, MMdM, Tussu, Mattia, Alberto and all of them, including the new born ones, who are spicing up our days and make me a proud Auntie Cinciu.

Questi anni ad Amburgo non sarebbero stati gli stessi senza Marta, Ana, Isa e tutti coloro che sono comparsi e scomparsi tra i vari weekend divisi tra la Comfort Zone e Mio Gelato cercando di sopravvivere, integrarsi e mantenere le nostre unicità. Grazie agli italiani conosciuti nelle stesse occasioni, compagni di avventure tricolori. Un grazie anche a Luisa per avermi aiutata ad integrarmi nella sua patria.

Se sono arrivata fino a qua è stato anche grazie alla parentesi di Ulm, a Ulli, Paula ed Eva. Al loro supporto e incoraggiamento, oltre che ad avermi dato una casa in più di cui sentire la mancanza. Un grazie alla mia variopinta Ulmer Family: Srihari, Erica, Jennia, Noemi, Marion, Rodrigo, Matheus e Rebecca, alle stupende serate con loro. Ai Latinos: Kleber, Javi ed Emmanuel e alle serate ignoranti e ai discorsi importanti. E a quel qualcuno (Joe) che mi ha ricordato un lunedì sera al MoBar che quando niente è certo, tutto è possibile, anche trovare un lavoro di quelli veri.

E poi a tutti quelli che ci sono sempre stati e continueranno ad esserci. E anche a quelli che ci sono stati ma si sono persi, ma non per questo meno importanti.
A Casa K. (Aly e Sara in rappresentanza), a quelli dell'università (Fabio, Cesare, Vale, Mary..) a Trieste generalmente parlando (Mario).
A Isa, Stella e Robi.
Al Friuli, alla mie radici, da sempre troppo strette ma con un enorme posto nel mio cuore: Noni, Pince, Chiara, Sara, Linas, Lele, Trac, Slobbe, Greg, Dani, Giorgino, Tuiter, MMdM, Tussu, Mattia, Alberto e tutti loro, inclusi i nuovi piccoli arrivati, che colorano le nostre giornate e mi rendono una fiera Zia Cinciu.

To Martina, to have helped me when I was not asking for it and saved me letting me save her, because sometimes a bicycle and some laughs are enough, and because even if we grow up we never really change. And because a house is useless, if is empty.

A Martina per avermi aiutato quando non lo chiedevo e salvato facendosi salvare, perché a volte basta una bici e una risata, perché pur crescendo non si cambia mai davvero. E perché è inutile averla una casa, se è vuota.

To the “brothers who have found themselves again” and to the ones who never got lost, my two families, that mix of chaos, yells and loud opinions, followed by good food and something strong to drink. Because sometimes is beautiful to just be ourselves, with all the facets.

Ai “fratelli ritrovati” e a quelli che non si sono mai persi, le mie due famiglie, quel mix di chaos, urla e opinioni gridate accompagnate da buon cibo e qualcosa di forte da bere. Perché a volte è bello anche essere semplicemente se stessi, con tutte le sfaccettature.

To my brother Marco, because being good is the only investment which will never fail.

A mio fratello Marco, perché la bontà è l’unico investimento che non fallisce mai.

To my parents that didn’t hesitate to get on plane to come visiting me, because sometimes is a bolder choice to let go than to leave.

Ai miei genitori per non aver esitato a salire su un aereo per venirmi a trovare, che a volte ci vuole più coraggio a lasciare andare che a partire.

To me, and I here I knowingly repeat myself, who has never gave up on believing, fighting and smiling.

E poi, e qui lo so mi ripeto, a me, che non ho mai smesso di crederci, di lottare e di sorridere.

Thank you from the bottom of my heart, thank you for making me happy, because it is the only thing that matters.

Grazie di cuore e grazie di rendermi felice, perché alla fine è l’unica cosa che conta.

Thanks.

Grazie.

Danke.

Gracias.

Obrigada.

Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Hamburg, 13/07/2018

_____

Silvia Londero