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Guideline on Manufacture of the Veterinary Finished Dosage Form

Draft

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This guideline replaces the Veterinary “Note for Guidance on Manufacture of the Finished Dosage Form” (EMA/CVMP/126/95)

Comments should be provided using this [template](#). The completed comments form should be sent to vet-guidelines@ema.europa.eu

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¹ In view of the suspension of guideline work from 1 October 2018, as part of the Agency's business continuity plan, the consultation period has been extended and will finish at the end of August 2019 when the CVMP working party activities are expected to resume.



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1 Executive summary

2 This guideline replaces the veterinary note for guidance on the manufacture of the finished dosage
3 form (EMA/CVMP/126/95). The note for guidance has been updated to reflect the requirements as
4 laid down in the current legislation (Directive 2001/82/EC, as amended and its Annex I (ref. 1, ref. 2
5 respectively)). It also addresses current manufacturing practices in terms of complex supply chains
6 and worldwide manufacture.

7 In addition, applicants for EU marketing authorisations (MAs) of veterinary medicinal products may
8 voluntarily choose to follow enhanced concepts in the manufacturing process of the final dosage forms
9 as outlined in the ICH guidelines Q8, Q9 and Q10 (formally applicable to medicinal products for
10 human use, refs 3, 4 and 5 respectively). The revised guideline takes this option into account
11 although it is highlighted that the traditional approach is still acceptable.

12 This guideline does not introduce new requirements for authorised medicinal products for veterinary
13 use. However as stated in Article 27 of Directive 2001/82/EC as amended, after a marketing
14 authorisation has been approved, the authorisation holder should, in respect of the methods of
15 manufacture and control, take account of scientific and technical progress and introduce any changes
16 that may be required to enable the medicinal product to be manufactured and controlled by means of
17 generally accepted scientific methods.
18

19 1. Introduction (background)

20 The objective of this guideline on the manufacture of the finished dosage form is to provide
21 clarification on the type and level of information that should be included in the Part 2 (CTD Module 3)
22 of the marketing authorisation application (MAA) dossier with respect to the manufacturing process
23 description. This description should include information about critical steps and intermediates and
24 provide a link between the pharmaceutical development, the proposed control strategy and process
25 validation. The guideline also addresses aspects related to outsourcing and new manufacturing
26 practices such as complex manufacturing chains or issues with prolonged holding times and
27 transportation conditions. Detailed information about requirements of any sterilisation process is
28 provided in a separate guideline.

29 2. Scope

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

34 The principles described are in general also applicable to veterinary medicinal products which include
35 biological active substances, but not to immunological products.

36 3. Legal basis

37 This guideline should be read in conjunction with Directive 2001/82/EC Article 12.3(d) as amended
38 where it is stated that the application for a marketing authorisation shall contain a description of the
39 manufacturing method.

40 The requirements for the description of the manufacturing method in the Part 2 of a marketing
41 authorisation dossier are described in Annex 1, Title 1 (Part 2.B and 2.D) of this Directive. Further
42 details on the information to be provided are outlined in this guideline.

43 4. Manufacture

44 Sections 4.1 to 4.3 of this guideline should be reflected in the contents of Part 2.B., and section 4.4 in
45 Part 2.D of the MA dossier. However where the CTD format is accepted, it should be noted that the
46 headings of this guideline follow the structure of the CTD format Module 3, Section 3.2.P.3
47 Manufacture.

48 Only product specific aspects of manufacture need to be described and included in the MA dossier;
49 general elements of Good Manufacturing Practice (GMP), (ref. 6) should not be included.

50 4.1. *Manufacturer(s)*

51 For each stage of the manufacturing process, including packaging, details should be given of all
52 the individual sites involved (including those from the same company).

53 The name, address and responsibility of each manufacturer, including contractors, should be
54 provided. This applies also to all quality control sites, including on-going stability testing if different
55 from the manufacturing site(s).

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

57 4.2. *Batch Formula*

58 The batch formula for the intended batch size should be stated. In case a range of batch sizes is
59 proposed, the range should be stated and the batch formula should be provided for at least the
60 largest and smallest batch sizes.

61 An application for a range of batch sizes should be adequately justified as not adversely impacting the
62 critical quality attributes (CQAs) of the finished product in accordance with the guideline on process
63 validation (ref. 7).

64 If the bulk product is assembled into different presentations or packs, the production batch size
65 should be defined by the bulk before any division. When the length of the subsequent processes and
66 assembly is considered critical (e.g. filling time for aseptically manufactured products), the worst-case
67 scenario of the division pattern (e.g. in respect of total filling time) should be indicated.

68 The batch size for a product to be marketed should normally be compatible with production scale
69 equipment. It should be sufficiently large to be representative of commercial manufacturing to enable
70 demonstration of a state of control. For example, a commercial batch size for solid oral dosage forms
71 should be at least 100,000 units unless justification is provided (ref. 7).

72 If sub-batches are prepared and combined for subsequent processing, this should be justified as the
73 final batch is required to be homogeneous, their formulae and the number of sub-batches per intended
74 batch size should be stated. In addition, if a batch is sub-divided towards the end of the process to
75 reflect equipment processing capability, this should be clearly indicated (e.g. solid dosage form
76 manufacture where sub lots are required due to equipment capacity). The number of sub-batches per
77 intended batch size should be stated.

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

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

85 Ingredients that are optionally used, such as acids and alkalis for pH adjustment, should also be
86 mentioned. Formula overages must be clearly indicated in quantitative terms and justified in the
87 pharmaceutical development part of the dossier. Upper and lower acceptance limits for the actual
88 quantity of each ingredient may be stated in the batch formula; however, the proposed acceptance
89 limits should be justified. When the quantity of an active ingredient to be used is calculated from the
90 actual assay value of the batch of that active ingredient ("factorisation"), this should be stated and
91 justified. If another ingredient is used to keep the total mass per batch equal to the quantity provided
92 for in the batch manufacturing formula, this should also be indicated.

93 *4.3. Description of Manufacturing Process and Process Controls*

94 General aspects

95 A narrative description of the full manufacturing process should be provided, accompanied by a flow
96 chart describing each step of the process including in-process controls and showing at each stage
97 where materials enter the process. In case a design space is proposed, this should be clearly
98 identified and described.

99 The manufacturing process description should be adequately justified in Part 2.A.4 (CTD 3.2.P.2) by
100 development data, in particular as regards any process operating conditions or ranges. The
101 description of a manufacturing process with wide ranges (wider than would normally be accepted as
102 normal operating ranges) or described only by an upper or lower limit, generally requires a more
103 thorough discussion and/or scientific rationale in the manufacturing process development part.

104 Full scale manufacturing process validation is not requested at the time of application for certain types
105 of products (ref. 7). If the results of such full scale studies are not available at the time of submission,
106 it is expected that process parameters' settings identified during manufacturing process development
107 are laid down in the process description. In the event that any changes are required to the registered
108 process parameters as a result of full scale process validation studies, these changes should be
109 applied for via post approval variation, in accordance with the variation Regulation (ref. 8, ref. 9).

110 Where specifically relevant for the product, any required environmental conditions during manufacture
111 should be stated e.g. low humidity for a foaming intrauterine tablet.

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

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

116 Consideration should be given in Part 2.A.4 (CTD 3.2.P.2) to what extent the assurance of quality of
117 the finished product is founded on the manufacturing process itself. The significance of the process
118 description and process controls as part of the overall control strategy should be outlined based on
119 development studies and evaluated. Indeed, every finished product manufacturing process should
120 have an associated control strategy suitable for its intended purpose. It is expected that different
121 control strategies may be utilised if parametric release (ref. 10) or real time release testing (RTRT)
122 (ref. 11) is proposed, a design space is claimed (ref. 3), or continuous manufacture or a standard
123 manufacture is performed.

124 Expected level of detail in the manufacturing process description

125 Although it is expected that the process description is considered in relation to the control strategy
126 (ref. 3), there is a need to describe the manufacturing process in relevant detail since consistent
127 quality of a product cannot be safeguarded by end product testing alone.

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

143 The same requirements apply to the level of detail in the manufacturing process description
144 irrespective of the development approach, i.e., if the product has been developed by the traditional or
145 an enhanced approach.

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

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

150 Technical adaptations in the manufacturing process

151 It would generally be expected that, regardless of the number of finished product manufacturing sites
152 proposed, essentially the same manufacturing process should be applied for a specific veterinary
153 medicinal product. However, some technical adaptations might be necessary if more than one
154 manufacturer or manufacturing site for the finished product is foreseen. Technical adaptations are
155 equally acceptable within a manufacturer/ manufacturing site given appropriate justification. Depending

156 upon equipment availability, different types of equipment could be used for the same manufacturing
157 processing step.

158 Where technical adaptations are proposed in the manufacturing process, these adaptations should be
159 fully justified and supported by evidence, showing that all steps proposed will consistently produce
160 any intermediate and finished product that comply with the in-process controls and the product
161 specifications. Irrespective of any differences in the manufacturing process, the finished product
162 should comply with the same release and shelf life specifications.

163 Where relevant, the justified technical adaptations in various steps of the manufacturing process of
164 one or more manufacturers and corresponding in-process controls should also be transparently shown
165 in separate flow-charts. If separate flow-charts are presented in a dossier the different manufacturing
166 steps should be listed and the adaptations should be compared to each other by the applicant. The
167 applicant should justify that the adaptation(s) for using different types of equipment do not have any
168 significant influence on the finished product quality and this should be supported by data. The in-
169 process controls and corresponding acceptance limits should also be described. Where any technical
170 adaptations are proposed at different manufacturing sites, the information should always be
171 presented in the same part of the dossier, but if required, differentiated for each manufacturing site.

172 The following examples illustrate the possible use of technical adaptations for different manufacturing
173 processing steps:

174 Liquid dosage forms

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

177 Solid oral dosage forms

178 Different equipment can be used for:

- 179 • Wet granulation (wet granulation by high shear -, low shear - or fluid bed granulation);
- 180 • Granule drying (e.g. fluid bed -, tray drying, one pot (high shear granulation/drying) systems);
- 181 • Dry granulation (roller compaction or slugging);
- 182 • Sizing/delumping (e.g. oscillating -, rotating - or hammer mill);
- 183 • Coating (e.g. pan -, fluidized bed coating);
- 184 • Dry blending (e.g. high shear blender, IBC blender, conical screw blender, V-blender);
- 185 • Tablet compression on a fully automatic or manually controlled tablet press.

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

192 Control of critical steps

193 For complex control strategies (e.g. use of models for process control, continuous manufacturing),
194 emphasis should be given on the frequency of in-process controls and it should be clearly stated how

195 release testing and product release decisions are made. Information of how unexpected deviations
196 from the approved manufacturing process would be detected and managed should be provided to
197 assure that the intended quality of the product is retained.

198 The fact that a process parameter in a manufacturing step is controlled and verified to be within a
199 range that does not affect a critical quality attribute (CQA) does not make it non-critical by default.
200 While the risk is reduced, monitoring with established acceptance criteria should be included in the
201 description to assure a sufficient regulatory oversight. The justification for the identification of steps
202 as critical or non-critical should be provided, including a link to experimental data in the
203 pharmaceutical development part (e.g. risk assessment table), if applicable.

204 *4.4. Controls of Intermediates*

205 All intermediates identified during the manufacture of the finished product should be listed in Part 2.D
206 (CTD 3.2.P.3.4) including any applied test methods and acceptance criteria.

207 Storage of intermediate and bulk products

208 An intermediate product is defined as partly processed material that must undergo further
209 manufacturing steps before it becomes bulk product.

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

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

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

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

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

230 The reasons for any prolonged storage/processing times should be stated and be consistent with GMP.
231 Time limits for processing should be minimised and limits should be justified and appropriate to
232 ensure product quality. As a general rule, prolonged storage means more than 30 days for solid oral
233 dosage forms and more than 24 hours for sterile products. Where relevant, stability data to support
234 the holding time should be provided on at least two pilot scale batches. The stability studies should be
235 performed using temperature(s) and humidity(ies) relevant to the expected bulk storage conditions (if

236 the relevant temperature and humidity during storage does not correspond with VICH conditions,
237 other conditions should be used).

238 The product shelf life should be calculated according to the Note for Guidance on the start of shelf life
239 of the finished dosage form (ref. 13). If other approaches to calculate the start of shelf life are
240 proposed, these should be described and justified by the inclusion of supporting data from batches
241 that represent the full proposed holding time of the bulk product (intermediate) in the finished
242 product stability program.

243 For the transportation of bulk product (intermediate) between manufacturing sites, guidance is given
244 in GMP Annex 15 on how transport should be taken into consideration. The impact of short or longer
245 excursions outside of the original storage conditions should be discussed, where necessary, supported
246 by accelerated or real time stability data.

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

251 *4.5. Process Validation and/or Evaluation*

252 Description, documentation, and results of the validation and/or evaluation studies should be
253 provided in Part 2.B. For more details see the Process Validation guideline (ref. 7).

254 Definitions

255 Control Strategy:

256 A planned set of controls, derived from current product and process understanding that ensures
257 process performance and product quality. The controls can include parameters and attributes related to
258 drug substance and drug product materials and components, facility and equipment operating
259 conditions, in-process controls, finished product specifications, and the associated methods and
260 frequency of monitoring and control (ref. 5).

261 Critical Process Parameter (CPP):

262 A process parameter whose variability has an impact on a critical quality attribute and therefore should
263 be monitored or controlled to ensure the process produces the desired quality (ref. 3).

264 Critical Quality Attribute (CQA):

265 A physical, chemical, biological or microbiological property or characteristic that should be within an
266 appropriate limit, range, or distribution to ensure the desired product quality (ref. 3).

267 Design Space:

268 The multidimensional combination and interaction of input variables (e.g., material attributes) and
269 process parameters that have been demonstrated to provide assurance of quality. Working within the
270 design space is not considered as a change. Movement out of the design space is considered to be a

271 change and would normally initiate a regulatory post approval change process. Design space is
272 proposed by the applicant and is subject to regulatory assessment and approval (ref. 3).

273 **Hold Time:**

274 Hold time can be considered as the established time period for which materials (dispensed raw
275 materials, intermediates and bulk dosage form awaiting final packaging) may be held under specified
276 conditions and will remain within the defined specifications (ref. 13).

277 **Parametric release:**

278 Parametric release is a system of release that gives the assurance that the product is of the intended
279 quality based on information collected during the manufacturing process and on the compliance with
280 specific GMP requirements related to Parametric Release (ref. 10).

281 **Real Time Release Testing:**

282 The ability to evaluate and ensure the quality of in-process and/or final product based on process data,
283 which typically include a valid combination of measured material attributes and process controls
284 (ref. 3).

285 References

- 286 1. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the
287 Community code relating to veterinary medicinal products, as amended;
- 288 2. Directive 2009/9/EC (i.e. Annex I to the Directive 2001/82/EC);
- 289 3. ICH Q8 (R2) (Pharmaceutical development) (EMA/CHMP/ICH/167068/2004);
- 290 4. ICH Q9 Quality Risk Management (EMA/CHMP/ICH/24235/2006);
- 291 5. ICH Q10 Pharmaceutical Quality Systems (EMA/CHMP/ICH/214732/2007);
- 292 6. EudraLex volume 4 (GMP guidelines);
- 293 7. Guideline on process validation for finished products - information and data to be provided in
294 regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012 Rev. 1);
- 295 8. Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms
296 of marketing authorisations for medicinal products for human use and veterinary medicinal
297 products;
- 298 9. Guidelines on the details of the various categories of variations, on the operation of the procedures
299 laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24
300 November 2008 concerning the examination of variations to the terms of marketing authorisations
301 for medicinal products for human use and veterinary medicinal products and on the documentation
302 to be submitted pursuant to those procedures;
- 303 10. Guideline on Parametric Release (EMA/CVMP/QWP/339588/2005);
- 304 11. Guideline on Real time release testing (EMA/CHMP/QWP/811210/2009-Rev1);
- 305 12. Note for guidance on the start of shelf-life of the finished dosage form (CPMP/QWP/072/96,
306 EMA/CVMP/453/01);
- 307 13. Supplementary guidelines on GMP: General guidance on hold-time studies. In: WHO Expert,
308 Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World
309 Health Organization; 2015: Annex 4 (WHO Technical Report Series, No. 992)

310 Annex

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

317 To explain the description presented in Part 2.B (CTD 3.2.P.3.3.) (starts with Narrative
318 description), some elements from manufacturing process development are reproduced below:

319 Finished product: 200 mg tablet

320 Process step: granulation

321 Operating principle: wet high shear granulation

322 Equipment type: vertical high shear granulator

323

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

- 326 • Delumping sieve size.
- 327 • Mixing time for granulation solution preparation.
- 328 • Mixing speed for granulation solution preparation.
- 329 • Fill volume.
- 330 • Premix time.
- 331 • Premix impeller speed.
- 332 • Premix chopper speed.
- 333 • Granulation solution pressure.
- 334 • Granulation solution feed pump speed.
- 335 • Granulation solution flow rate.
- 336 • Granulation solution amount.
- 337 • Impeller rotation speed for the different granulation phases.
- 338 • Chopper rotation speed for the different granulation phases.
- 339 • Wet massing time.
- 340 • Product temperature.
- 341 • Wet mass screen size.

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

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

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

- 348 • Fill volume.
- 349 • Premix time.
- 350 • Granulation solution flow rate.
- 351 • Granulation solution amount.
- 352 • Impeller rotation speed for the different phases.
- 353 • Chopper rotation speed for the different phases.
- 354 • Wet massing time.
- 355 • Wet mass screen size.

356 Part 2.B (CTD 3.2.P.3.3.)

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

- 358 1. Weigh and delump the required amount of active substance and intra-granular excipients.
- 359 2. Weigh the required amount of binder excipient and purified water; charge the purified water in a
360 mixing vessel and dissolve the binder excipient; mix until a clear solution is obtained.
- 361 3. Load active substance, intra-granular excipient 1, intra-granular excipient 2 and intra-granular
362 excipient 3 in the bowl of the high shear mixer granulator.
- 363 4. Mix the dry material.
- 364 5. Wet the dry mix (from step 4) with the granulation solution (from step 2) added by fine
365 atomization through a binary nozzle.
- 366 6. Wet mass the blend with impeller.
- 367 7. Screen the wet mass through in-line sizing mill unit and transfer to fluid bed dryer.

368

369 Process parameters settings (traditional development approach):

Process step #	Parameter	Target value or range
3/ Loading	Fill volume	30% w/v
4/ Pre mixing	Time	2 minutes (1 – 3 minutes)
5/ Granulation solution addition	Flow rate	9 kg/min
	Granulation solution amount [#]	15% w/w
	Impeller speed	90 rpm
	Chopper speed	0

	Time	3 minutes (2 – 4 minutes)
6/ Wet massing	Impeller speed	170 rpm
	Chopper speed	2000 rpm
	Time	5 minutes (4 – 6 minutes)
7/ Wet mass screening	Screen size	1 mm

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

372

373 Process parameters settings (enhanced development approach):

Process step #	Parameter	Criticality	Target value or range (*)
3/ Loading	Fill volume	Non CPP	30 – 50% w/v
4/ Pre mixing	Time	Non CPP	1 – 3 minutes
5/ Granulation solution addition	Flow rate	Non CPP	5 – 15 kg/min
	Granulation solution amount#	CPP	12 – 18% w/w
	Impeller speed	Non CPP	80 – 110 rpm
	Chopper speed	N/A	0
	Time	Non CPP	2 – 4 minutes
6/ Wet massing	Impeller speed	CPP	150 – 190 rpm
	Chopper speed	CPP	1800 – 2500 rpm
	Time	CPP	3 – 7 minutes
7/ Wet mass screening	Screen size	Non CPP	0.595 – 1.41 mm

374 *Ranges established on the basis of multivariate evaluation.

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

379 Notes for the above examples:

- 380 • The same basic requirements apply to the level of detail provided in terms of the manufacturing
381 processing steps and parameters listed in Part 2.B (CTD 3.2.P.3.3.) whatever the approach to
382 pharmaceutical development (traditional or enhanced). However, depending upon the level of
383 process understanding that has been gained during development and also the control strategy, the
384 way the information is presented may be slightly different and the manufacturing process will
385 reflect any justified and supported flexibilities when an enhanced development approach has been
386 followed (e.g. wide ranges established on a multivariate basis).
- 387 • The manufacturing process principle is described.
- 388 • The equipment type is described.
- 389 • Process parameters are described (with target values or ranges) leading to a comprehensive
390 description of the unit operation; for applications able to assign criticality to process parameters,
391 both critical and non-critical parameters are described.
- 392 • There is a reduced list of process parameters remaining in the description compared to the "early
393 development list" as the following has been taken into account:
 - 394 - Nature of the active substance (e.g. the active substance is chemically stable and thus there is
395 no need to describe the environmental and product temperatures);
 - 396 - Degree of complexity of the dosage form (e.g. the proportion of active substance in the tablet
397 formulation is high and thus there is no need to describe the pre mixing step in detail);
 - 398 - Degree of complexity of the process (e.g. the delumping of raw materials before processing is
399 an optional step and thus there is no need to describe the delumping sieve size; the
400 preparation of the binder solution is a straight forward operation which is merely monitored
401 by the visual control of the final solution thus there is no need to describe the mixing
402 parameters; the granulation solution addition is adequately summarized by the output "flow
403 rate" thus there is no need to describe the liquid pressure and the pump speed).