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4 **Guideline on process validation for the manufacture of**
5 **biotechnology-derived active substances and data to be**
6 **provided in the regulatory submission**
7 **Draft**

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8 Comments should be provided using this [template](#). The completed comments form should be sent
9 to BWPsecretariat@ema.europa.eu

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14 **Table of contents**

15	Table of contents	2
16	Executive summary	3
17	1. Introduction	3
18	2. Scope	3
19	3. Legal basis	4
20	4. Process development	4
21	5. Process validation	4
22	5.1. Process evaluation.....	4
23	5.2. Process verification.....	5
24	5.3. Ongoing process verification	6
25	6. Points to consider in process validation	6
26	6.1. Upstream process.....	6
27	6.2. Downstream process	8
28	6.3. Multifacility production	9
29	Definitions	10
30	References	11

31 **Executive summary**

32 The guideline covers process validation of biotechnology-derived proteins used as active substance in
33 the manufacture of medicinal products. This guideline addresses the data requirements for process
34 validation for submission of a marketing authorisation application or variation. Process Validation can
35 be based on a traditional or enhanced approach to process development. Traditional and enhanced
36 approaches are not mutually exclusive. A company can use either a traditional approach or an
37 enhanced approach to process validation, or a combination of both. Regardless of the approach
38 followed, the validation data to be included in the regulatory submission should cover information
39 relating to the evaluation and the verification of the manufacturing process.

40 **1. Introduction**

41 Process validation is the documented evidence that the process, operated within established
42 parameters, can perform effectively and reproducibly to produce an active substance or intermediate
43 meeting its predetermined specifications and quality attributes (ICH Q7).

44 Process validation studies should normally be completed and included in the marketing authorisation
45 application or a variation application if relevant. It is acknowledged that process validation activities do
46 not end at the time of the marketing authorisation, but continue through the lifecycle of the product
47 and its process. This document addresses the information expected to be presented in a regulatory
48 submission to demonstrate that the manufacturing process described in the Common Technical
49 Document (CTD) section *S.2.2 Description of manufacturing process and process controls* consistently
50 performs as intended. This information normally includes process evaluation and verification studies.

51 **Process evaluation** studies, performed at small and/or full scale, should **provide evidence** that the
52 complete manufacturing process and each step/operating unit have been appropriately designed and
53 are controlled to obtain a product of the intended quality.

54 **Process verification** studies should **confirm** that the final manufacturing process performs effectively
55 and is able to produce an active substance or intermediate meeting its predetermined acceptance
56 criteria, on an appropriate number of consecutive batches produced with the commercial process and
57 scale.

58 Subsequent to successful process validation activities for regulatory submission, product quality and
59 process performance must be maintained in a state of control throughout the commercial part of the
60 product lifecycle. These activities have to be performed in compliance with EU Good Manufacturing
61 Practices (GMP).

62 **2. Scope**

63 This document provides guidance on the data to be included in a regulatory submission to demonstrate
64 that the active substance manufacturing process is in a validated state. The principles adopted and
65 explained in this document apply to recombinant proteins and polypeptides, their derivatives, and
66 products of which they are components (e.g. conjugates), as defined in ICH Q6B.

67 The principles that are outlined in the document may also apply to other biological products such as
68 vaccines or blood products, as appropriate. To determine applicability, manufacturers should consult
69 with the appropriate regulatory authorities.

70 For evaluation of viral safety, please refer to ICH Q5A.

71 **3. Legal basis**

72 This guideline has to be read in conjunction with the introduction and general principles (4) and Part II
73 of Annex I to Directive 2001/83/EC as amended.

74 **4. Process development**

75 The goal of manufacturing process development for the active substance is to establish a commercial
76 manufacturing process capable of consistently producing an active substance of the intended quality.
77 Although not considered as part of process validation, process development comprises an essential role
78 in defining the criteria and conditions to be addressed in process validation studies. For further
79 information, please refer to ICH Q11 guideline.

80 Manufacturing process development should identify which inputs (e.g. material attributes, process
81 parameters) and outputs (e.g. quality attributes, process indicators) for each process step/unit
82 operation should be further evaluated during process validation studies.

83 Documented prior knowledge and risk assessment can help identify and justify the material attributes
84 (e.g. of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process
85 parameters with the potential for having an effect on active substance critical quality attributes (CQAs)
86 and/or process performance.

87 Process development information should usually be submitted in Section 3.2.S.2.6 of the CTD.

88 **5. Process validation**

89 A prospective process validation, as defined in ICH Q7, is expected for biotechnology-derived active
90 substances. Process validation activities would normally include *i)* evaluation that process steps and
91 the complete process are capable to perform as intended and *ii)* verification on commercial scale
92 batches that the process does perform as intended. The contribution of data from small scale studies
93 to the overall validation package will depend upon demonstration that the small scale model is an
94 appropriate representation of the proposed commercial scale. Successful demonstration of the
95 suitability of the small scale model could reduce data requirements for process verification (e.g.
96 reduced number of batches) and/or impact on control strategy (e.g. alternative approach to end
97 product testing, ongoing process verification) by evaluation and understanding of the sources of
98 variability of CQAs. This is further discussed below.

99 The set of controls used in process validation activities (e.g. quality attribute, process indicator,
100 process parameter, controls implicit in the design of the process) are expected to go beyond the
101 routine control system as described in S.2.2 and S.2.4.

102 Considering that evaluation and verification activities are often investigated in the same study, it is not
103 always necessary to make a difference between these activities as long as the evidences required for
104 their demonstration are appropriately presented.

105 Process validation information should usually be submitted in Section 3.2.S.2.5 of the CTD.

106 **5.1. Process evaluation**

107 Process evaluation studies should provide evidence that, when operating in accordance with the
108 *Description of manufacturing process and process controls (CTD section S.2.2)*, the complete
109 manufacturing process and each step/operating unit have been appropriately designed and controlled

110 to obtain a product of the intended quality. Successful process evaluation should thus demonstrate
111 that the design of the manufacturing process and its control are appropriate for commercial
112 manufacturing.

113 The applicant should base the inputs and outputs studied on their potential criticality and justify their
114 selection. For those which are not studied further it may be needed to explain how it is ascertained
115 that these are kept within the range that has been shown to be non-critical.

116 These studies should include the evaluation of the ability of each step to obtain a product or
117 intermediate of desired quality at small and/or full scale as appropriate, when operating in accordance
118 with the described process and process controls. The results of inputs and outputs should be presented
119 for each step. These data should demonstrate that when operating within the proposed input ranges,
120 the output meets relevant quality criteria (i.e. predefined acceptance criteria or internal limits), and
121 thus support the proven acceptable ranges (PAR). The outcome of the evaluation studies serves as the
122 main basis of defining the control strategy and also in setting the acceptance criteria for the
123 verification studies.

124 Where appropriate, evaluation of selected step(s) operating in worst case and/or abnormal conditions
125 (e.g. cumulative hold time, spiking challenge) could be performed to support or demonstrate the
126 robustness and the capability of the process to deliver product of the intended quality in these
127 conditions. In some cases, these activities could be built into process verification studies (e.g. lots
128 produced with intermediates stored in worst case hold conditions).

129 Small scale models are important tools in the development and evaluation of biopharmaceutical
130 manufacturing processes. During process evaluation, small scale models enable evaluation of input
131 material and parameter variability to an extent that may not be feasible at manufacturing scale. A
132 small scale model must be designed and executed, and ultimately demonstrated, as an appropriate
133 representation of the manufacturing process.

134 It is acknowledged that small scale models are incomplete representations of commercial scale
135 process. When used, small scale models should be described and their relevance for the commercial
136 scale should be justified, in terms of objective, design, inputs and outputs. When validation studies are
137 highly dependent on the small scale model studies (e.g. design space claimed), it may be necessary to
138 demonstrate that when operating under the same conditions using the same input materials, the
139 outputs resulting from the commercial scale process match those of the small scale model. Any
140 difference in operating conditions, inputs or outputs should be appropriately justified. Depending on
141 the differences observed and their understanding, approaches to manage these differences (e.g. use of
142 correction factors in cases where Design of Experiments is used) could be acceptable if well
143 documented and justified. The use of such an approach requires appropriate management of the risks
144 linked to this uncertainty (e.g. managed through control strategy).

145 Where prior knowledge or platform manufacturing experience is utilised, the contribution of these data
146 (e.g. to justify operating ranges, input set points) to the overall validation package will depend upon
147 justification that the data is representative of the proposed commercial process. Usually, full scale
148 validation studies should include data derived from the final manufacturing process and site(s) used to
149 produce the product to be commercialised.

150 **5.2. Process verification**

151 Process verification studies should confirm that the final manufacturing process (i.e. full scale
152 commercial process) performs effectively and is able to produce an active substance or intermediate

153 meeting its predetermined controls and acceptance criteria. Such studies are generally performed in
154 accordance to the expected normal operating ranges (NORs).

155 Process verification data (including process step results, batch analyses) should normally be completed
156 and presented in the regulatory submission on an appropriate number of consecutive batches produced
157 with the commercial process and scale, taking into account the batch definition as detailed in the
158 process description. Failure to present validation data on consecutive batches should be appropriately
159 justified. The number of batches to be presented depends on several factors including but not limited
160 to: (1) the complexity of the process being validated; (2) the level of process variability; (3) the
161 amount of experimental data and/or process knowledge available on the process; and (4) the
162 frequency and cause(s) of deviations and batch failure.

163 As an alternative approach, continuous process verification could facilitate acceptance of fewer batches
164 in the verification studies. The success of such an approach will be highly dependent on the knowledge
165 and understanding gained on the process and product, and the process analytical technologies
166 deployed to control and monitor the process inputs and outputs in an uninterrupted manner.

167 In the case that a design space is claimed, it may be needed to include a protocol on how movement
168 within the design space will be managed post approval to verify that the design space is still valid
169 when run at commercial scale. Please refer to ICH Q11 for further details.

170 **5.3. Ongoing process verification**

171 Subsequent to successful process validation activities for regulatory submission, companies should
172 monitor product quality and process performance to ensure that a state of control is maintained
173 throughout the commercial part of the product lifecycle. These activities have to be performed in
174 compliance with EU GMP, and should provide evidence of the continued capability of the process and
175 controls to produce product that meets the desired quality through the lifecycle of the product.

176 **6. Points to consider in process validation**

177 **6.1. Upstream process**

178 Process validation of the upstream process normally includes evaluation and verification that the cell
179 culture steps, from the introduction of the starting material in the manufacturing process (e.g. thaw of
180 the working cell bank (WCB)) up to the collection of the last harvest obtained at/or beyond production
181 level are capable to perform as intended.

182 Considering the complex matrices during cell culture and harvest steps, the evaluation/validation
183 could, in part, rely on the analysis of active substance and/or intermediates obtained at a later stage of
184 the process.

185 **6.1.1. Evaluation of upstream process**

186 Process evaluation activities should demonstrate that the cell culture steps, from the introduction of
187 the starting material in the manufacturing process (e.g. thaw of the WCB) up to and/or beyond
188 production level, are capable of consistently delivering inoculates, harvest(s), and ultimately an active
189 substance of appropriate quality. Several aspects should be considered when validating cell culture.
190 The level of detail provided should support the criticality assignment of process parameters.

191 These activities could include evaluation of specific cell traits or indices (e.g. morphological
192 characteristics, growth characteristics (population doubling level), cell number, viability, biochemical

193 markers, immunological markers, productivity of the desired product, oxygen or glucose consumption
194 rates, ammonia or lactate production rates), process parameters and operating conditions (e.g. time,
195 temperatures, agitation rates, working volumes, media feed, induction of production).

196 The conditions utilised to end fermentation/cell culture cycle and initiate harvest should be
197 appropriately defined and evaluated. Relevant information on the final culture steps (e.g. yield,
198 maximum generation number or population doubling level, consistency of cell growth, viability,
199 duration and microbial purity) should be presented.

200 Potential impact of raw materials (e.g. quality of media, supplements, treatment such as gamma
201 irradiation of animal sera) should be evaluated, in the light of the variability of these materials (e.g.
202 intrinsic to the material, related to change in supplier) and of their influence on the quality of the
203 product. Where appropriate, a risk-based approach could be presented to illustrate how variability of
204 these raw materials and their related risks are managed through the lifecycle of the product (e.g.
205 included in ongoing process verification protocol).

206 **6.1.2. Verification of upstream process**

207 Process verification activities should focus on the confirmation of consistency of performance indicators
208 and quality attributes when operating conditions and process parameters are in accordance to NORs.
209 These studies should include all culture steps and cover the complete duration of the process, on an
210 appropriate number of consecutive runs.

211 **6.1.3. General issues related to single use equipment**

212 When single use equipment is used, in development studies consideration should be given to
213 leachables and extractables. Information should be provided on the nature and amount of potential
214 leachables, their impact on the cell culture, and the removal of such impurities. Besides data this
215 normally includes a risk assessment. For validation full scale equipment has to be used. Various
216 batches of disposable systems should be used in the manufacturing of verification batches in order to
217 assess their impact on the product quality.

218 **6.1.4. General issues related to multiple harvests**

219 Where multiple harvests from one cell culture run are collected, it should be demonstrated that the
220 increasing cell age during the culture run does not have an impact on quality and intra-batch
221 consistency (i.e. derived from initial harvest through to last harvest) and inter-batch (i.e. derived from
222 different fermentation runs / cell culture cycles). Such evidence could be supported by appropriate
223 analysis of performance indicators (e.g. yield, titre) and quality attributes (e.g. post-translational
224 modifications, host cell proteins (HCP), DNA) which should be confirmed to be consistent throughout
225 the harvesting steps, otherwise an approach to manage the variability of harvests (e.g. by suitable
226 pooling strategy) should be proposed. As certain analyses of quality attributes (e.g. post-translational
227 modifications) may be difficult in a crude matrix, there may be a need for a partial, small scale
228 purification of single harvests representative of early, mid and late stages of the cell culture cycle, to
229 assess the effect of an aging cell population on the integrity of the product and to provide a scientific
230 basis for the establishment of termination criteria.

231 The verification of the consistency of batches based on several fermentations runs/ cell culture cycles
232 could lead to the necessity of producing a large number of batches spanning a long production period.
233 In such situation, an applicant may propose a protocol to verify the consistency of these batches
234 through ongoing process verification.

235 **6.2. Downstream process**

236 Downstream processing starts with the first step after final harvest and leads to a product of the
237 desired quality: it may include steps required for cell disruption, concentration of drug intermediates
238 and impurity clearance, polishing procedures but also protein refolding or potential modifications for
239 the protein of interest. Most frequently various chromatographic and filtration methods are applied. In
240 certain cases, specific steps aiming at a modification of the intermediate (e.g. conjugation to other
241 proteins, carbohydrates or chemicals, e.g. pegylation) are included.

242 **6.2.1. Evaluation of downstream process**

243 The capacity of the proposed purification procedures to deliver the desired product and to remove
244 product and process-related impurities (e.g. unwanted variants, HCPs, nucleic acids, media
245 components, viruses, reagents used in modification of the protein) to acceptable levels should be
246 thoroughly evaluated. This generally includes establishment of adequate analytical methods required
247 for their detection and an estimation of the concentrating or removing capacity for each unit operation
248 followed by the determination of appropriate acceptance criteria. For certain process-related impurities
249 (e.g. HCP, DNA, antibiotics) scale-down spiking experiments may be required to determine the
250 removal capacity of the individual purification steps. Evaluation of selected purification step(s) (e.g.
251 steps for which high impurity or viral clearance are claimed) operating in worst case and/or abnormal
252 conditions (e.g. cumulated hold times, spiking challenge) could be performed to document the
253 robustness of the process.

254 Process conditions (e.g. column loading capacity, flow rate, length, elution/washing conditions
255 conditions) and performance parameters/indicators (e.g. yield, chromatographic profiles) should be
256 appropriately evaluated.

257 In the case where feed forward and/or feedback loop systems are used to accommodate the conditions
258 of process steps, all claimed conditions should be appropriately evaluated regarding their impact on
259 output material(s), according to an appropriate design of experiments, and verified according to an
260 approved protocol.

261 Columns should also be evaluated throughout the expected lifetime of the column regarding
262 purification ability (e.g. clearance, collection of intended variants), leaching of ligands (e.g. dye,
263 affinity ligand) and/or chromatographic material (e.g. resin). Absence of specific leaching studies may
264 be acceptable for some resins with small molecule functional group, but requires appropriate
265 justification. Considering the number of purification cycles required for this evaluation, small scale
266 studies are considered appropriate to estimate and set the maximum number of cycles at the time of
267 regulatory submission, provided that full scale verification is performed on an ongoing basis, to confirm
268 the column performance and integrity, in accordance with an approved protocol.

269 **6.2.2. Verification of downstream process**

270 Verification activities should confirm the clearance capability of the entire downstream process,
271 showing that process parameters and performance indicators - in accordance to normal acceptable
272 ranges - are able to consistently generate the targeted quality of process intermediates and active
273 substance (i.e. appropriate purity/impurity profile for the given stage).

274 **6.2.3. Reprocessing**

275 Reprocessing, as defined in ICH Q7, could be considered in exceptional circumstances. For biological
276 products, these situations are usually restricted to some refiltration or re-concentration steps upon
277 technical failure of equipment. These steps should be appropriately described and validated in the
278 regulatory submission. Such documentation should include the demonstration that the reprocessing
279 step(s) do(es) not impact the quality of the active substance and the description of conditions for
280 which reprocessing could be applied (e.g. equipment failure). An essential prerequisite for the
281 acceptance of a reprocessing step is the clearly identified root cause.

282 **6.2.4. Hold time, storage and transportation**

283 Where hold times or storage are applied to process intermediates, the impact of the hold times and
284 conditions on the product quality should be appropriately evaluated. The evaluation should be
285 conducted as real-time, real-conditions studies, usually on commercial scale material. However, lab-
286 scale studies could additionally be considered if appropriately justified. A selection of stability indicating
287 assays and parameters addressing for example the biological activity, protein aggregation and
288 degradation, pH and bioburden should be applied in order to justify a maximum hold time for each
289 process step.

290 Studies conducted under worst case conditions and/or abnormal conditions (e.g. higher temperature,
291 longer time) could be used to further support the suitability of the claimed conditions.

292 The suitability of the studies to support the claimed cumulative hold time should be discussed by the
293 applicant. Provided the intermediate is stable and allows meaningful analyses, studies of separate
294 steps are likely to be sufficient.

295 Shipping and transportation of intermediates and active substance should be validated. Such study
296 should include demonstration that the quality of the intermediate or active substance will not be
297 altered if transported according to the defined conditions. A short summary of the study should be
298 provided in the dossier.

299 **6.3. Multifacility production**

300 During the lifecycle of biotechnological medicinal products, authorisation of additional manufacturing
301 sites may be required to meet market demand. The process established at the new site generally
302 requires technical adaptations of the approved process (e.g. scale up, different filters) in order to
303 accommodate the equipment and provisions of the additional site. The adapted process should be
304 capable of achieving comparable outputs when operating within the same input ranges.

305 In addition to the successful demonstration of comparability of products manufactured from the
306 different sites, it must be demonstrated that the subsequent site has reached a validated state.

307 The relevance of previous validation studies should be discussed. Where appropriate, it may be
308 necessary to re-demonstrate that models perform as expected. There is normally no expectation to re-
309 evaluate the complete process (e.g. clearance of impurities). Nevertheless, process verification studies
310 should be part of the submission. Depending on the differences between the sites and the
311 demonstration that previous validation studies are suitable representation of the new site, the ongoing
312 process verification could reduce the amount of process verification data to be submitted.

313 Optimisations of the production by using new processes (e.g. addition of new purification steps,
314 replacement of one step with another (such as size-exclusion chromatography with ion exchange

315 chromatography), different conditions in buffers) is considered to constitute an alternate process and is
316 not allowed within the same marketing authorisation.

317 **Definitions**

318 **Continuous process verification**

319 An alternative approach to process validation in which manufacturing process performance is
320 continuously monitored and evaluated (ICH Q8).

321 **Control strategy**

322 A planned set of controls, derived from current product and process understanding that ensures
323 process performance and product quality. The controls can include parameters and attributes related
324 to active substance and finished product materials and components, facility and equipment operating
325 conditions, in-process controls, finished product specifications, and the associated methods and
326 frequency of monitoring and control (ICH Q10).

327 **Feedback**

328 The modification or control of a process or a system based on its results and effects.

329 **Feed forward**

330 The modification or control of a process or a system using its anticipated results or effects.

331 **Feed forward and/or feedback loop**

332 Adjustments to the process based on feed forward or feedback information.

333 **High-impact model**

334 A model can be considered high-impact if prediction from the model is a significant indicator of quality
335 of the product.

336 **Normal operating range (NOR)**

337 The NOR describes a region around the target operating conditions that contains typical operational
338 variability and is within the claimed acceptable ranges. As such NORs themselves are not expected to
339 be submitted in the dossier for a biological product.

340 **Ongoing process verification**

341 Documented evidence that the process remains in a state of control during commercial manufacture.

342 **Platform manufacturing**

343 The approach of developing a production strategy for a new drug starting from manufacturing
344 processes similar to those used by the same applicant to manufacture other drugs of the same type
345 (e.g. as in the production of monoclonal antibodies using predefined host cell, cell culture, and
346 purification processes, for which there already exists considerable experience).

347 **Process validation**

348 The documented evidence that the process, operated within established parameters, can perform
349 effectively and reproducibly to produce a medicinal product meeting its predetermined specifications
350 and quality attributes.

351 **Process evaluation**

352 Studies, performed at small and/or full scale, should **provide evidence** that the complete
353 manufacturing process and each step/operating unit have been appropriately designed and are
354 controlled to obtain a product of the intended quality.

355 **Process verification**

356 Studies which should **confirm** that the final manufacturing process performs effectively and is able to
357 produce an active substance or intermediate meeting its predetermined acceptance criteria, on an
358 appropriate number of consecutive batches produced with the commercial process and scale.

359 **References**

360 ICH Q5A (R1) Guideline on quality of biotechnological products: viral safety evaluation of biotechnology
361 products derived from cell lines of human or animal origin (CPMP/ICH/295/95)

362 ICH Q6B Guideline on specifications: test procedures and acceptance criteria for biotechnological
363 /biological products (CPMP/ICH/365/96)

364 ICH Q7 Guideline on good manufacturing practice for active pharmaceutical ingredients
365 (CPMP/ICH/4106/00)

366 ICH Q10 Guideline on Pharmaceutical quality system (EMA/INS/GMP/79818/2011)

367 ICH Q11 Guideline on development and manufacture of drug substances (chemical entities and
368 biotechnological/biological entities) (EMA/CHMP/ICH/425213/2011)