



1 2 February 2021
2 EMA/CHMP/BWP/QWP/IWG/694114/2019
3 Committee for Human Medicinal Products (CHMP)

4 **Draft toolbox guidance on scientific elements and**
5 **regulatory tools to support quality data packages for**
6 **PRIME marketing authorisation applications**
7

Consultation with BWP, QWP, IWG and CAT	September 2020
Draft adopted by BWP, QWP, IWG and CAT	December 2020
Draft adopted by CHMP for release for consultation	29 January 2021
Start of public consultation	2 February 2021
End of consultation (deadline for comments)	31 July 2021

8

9

10

11 Comments should be provided using this [template](#). The completed comments form should be sent to
12 QWP@ema.europa.eu

13

14

15

16

Keywords	<i>Priority Medicines (PRIME), quality development, Module 3, data, scientific elements, regulatory tools, flexibility, benefit-risk</i>
-----------------	---

17



18	Table of contents	
19	Executive Summary	3
20	1. Introduction (background)	3
21	2. Scope	4
22	3. Legal and regulatory basis	5
23	4. Scientific Tools	6
24	4.1. Introduction.....	6
25	4.2. General scientific tools	6
26	4.2.1. Prior knowledge.....	6
27	4.2.2. Risk assessment.....	6
28	4.3. Scientific tools related to process validation	7
29	4.3.1. Process validation protocols	7
30	4.3.2. Concurrent validation	8
31	4.3.3. Deferral of the submission of certain process validation data.....	9
32	4.3.4. Decoupling active substance and finished product process validation.....	9
33	4.3.5. Continuous process verification	9
34	4.4. Scientific tools related to control strategy	10
35	4.4.1. Initial filing with a more “constrained” control strategy.....	10
36	4.4.2. The acceptance and use of <i>in-silico</i> models and purge factor calculations.....	10
37	4.4.3. Front-loading of control strategy activities/ CMC development plan.....	11
38	4.5. Approaches related to GMP compliance	12
39	4.5.1 Launching from an investigational medicinal product site.....	12
40	4.5.2 Alignment of quality review and GMP inspections.....	12
41	4.5.3 Use of biological starting material manufactured under a lower level of GMP	12
42	4.6. Scientific tools related to stability	13
43	4.6.1. Stability models generated from stability of structurally similar molecules (Biotech). 13	
44	4.6.2. Stability based on supportive knowledge (small molecules).....	14
45	4.7. Scientific tools related to comparability (biologicals)	14
46	4.7.1. Using prior knowledge to tailor comparability studies	14
47	4.7.2. Risk based identification of CQAs	15
48	4.7.3. Separate assessment of individual changes.....	15
49	4.7.4. Statistical tools for comparability	16
50	4.7.5. Comparability and Stability	16
51	4.7.6. Comparability for ATMPs.....	16
52	4.7.7. Need for additional (non)clinical data	16
53	5. Regulatory tools	17
54	5.1. Introduction.....	17
55	5.2. Regulatory tool 1: accelerated assessment	17
56	5.3. Regulatory tool 2: conditional marketing authorisation (CMA)	18
57	5.4. Other regulatory tools:.....	18
58	Post-approval change management protocols (PACMPs)	18
59	Post-authorisation measures (PAMs)	19
60	References	19

61 **Executive Summary**

62 The Priority Medicines (PRIME) scheme was launched to enhance EMA support to the development of
63 medicines that target an unmet medical need with the aim to help patients to benefit from these
64 therapies as early as possible. This is achieved by optimising the medicines development plans and
65 speeding up their evaluation.

66 Experience to date has shown that applicants face challenges to complete quality and manufacturing
67 development and data requirements during development of medicines for early access. This document
68 provides guidance, in a 'toolbox approach', by summarising scientific elements and regulatory tools,
69 available in the existing EU regulatory framework, that can be applied to support the development and
70 completion of Module 3 quality data packages in the preparation of marketing authorisation
71 applications (MAA) of designated PRIME medicinal products.

72 This toolbox guidance follows on from the Workshop with stakeholders on support to quality
73 development in early access approaches (i.e. PRIME, Breakthrough Therapies)¹, held jointly with the
74 US Food and Drug Administration (FDA) on 26 November 2018, which sought to identify scientific and
75 regulatory solutions to challenges commonly experienced by Applicants of PRIME applications in
76 completing Module 3 data requirements in time for the MAA.

77 **1. Introduction (background)**

78 The European Medicines Agency (EMA) launched the PRIME scheme to enhance support for the
79 development of medicines that target an unmet medical need. This voluntary scheme is based on
80 enhanced interaction and early dialogue with developers of promising medicines, to optimise
81 development plans and speed up evaluation so these medicines can reach patients earlier.

82 To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical
83 needs based on early clinical data.

84 Once a candidate medicine has been selected for PRIME, the Agency will:

- 85 • appoint a rapporteur from the Committee for Medicinal Products for Human Use (CHMP) or
86 from the Committee on Advanced Therapies (CAT) in the case of an advanced therapy to
87 provide continuous support and help to build knowledge ahead of a marketing-authorisation
88 application;
- 89 • assign a dedicated contact point from EMA and a dedicated EMA Quality specialist. Other team
90 support will be involved as needed (e.g. Inspections Office)
- 91 • organise a kick-off meeting with the CHMP/CAT rapporteur and a multidisciplinary group of
92 experts, so that they provide guidance on the overall development plan and regulatory
93 strategy;
- 94 • provide scientific advice at key development milestones, involving additional stakeholders such
95 as health-technology-assessment bodies, to facilitate quicker access for patients to the new
96 medicine;
- 97 • review the available information on supply chain to establish the need for an inspection and to
98 co-ordinate any inspections during the assessment;

¹ Stakeholder workshop on support to quality development in early access approaches, such as PRIME and Breakthrough Therapies (<https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough>)

- 99 • confirm potential for accelerated assessment at the time of an application for marketing
100 authorisation.

101 Experience to date has shown that applicants face challenges to complete quality and manufacturing
102 development and data requirements during development of products in early access approaches.

103 In order to address and overcome these challenges, the Agency wishes to support applicants with
104 guidance regarding their pharmaceutical development programme and flexibility on the provision and
105 type of data packages in the context of a MAA taking into consideration the overall benefit/risk of the
106 product. Specific guidance includes product characterisation, specification setting, validation and
107 stability testing as well as early identification of quality issues / attributes that are critical to the clinical
108 use of the medicinal product.

109 This toolbox guidance summarises scientific and regulatory approaches which can be considered and
110 applied by Applicants, tailored to their product development in question, to facilitate the development
111 and preparation of robust quality data packages. A well prepared and robust Module 3 will support
112 timely access to the medicine for patients whilst providing assurance that product quality and efficacy
113 and patient safety are not compromised. Similarly, applicants should ensure that manufacturers are
114 compliant with EU GMP and are inspection ready at the time of submission.

115 The scientific and regulatory approaches described in this document can offer flexibility in terms of the
116 time point for full completion of certain quality data packages when there is an unmet medical need
117 and should always be considered in the context of the specific benefit/risk of the product.

118 Nevertheless, while regulatory tools can support timely access, they do not reduce the product quality
119 requirements in a MA dossier. The data needed to demonstrate quality, safety and efficacy in line with
120 Annex I of Directive 2001/83/EC is expected to be provided in the MAA dossier.

121 Therefore, Module 3 marketing authorisation dossier data requirements must be in line with scientific
122 guidelines and technical requirements according to the EU legislation (Annex I of Dir. 2001/83/EC).
123 Alternative data sources (e.g. platform/pilot scale data) can be considered provided their relevance to
124 the product in question is established. In case of ATMPs, the content of the application can be adapted
125 under a risk-based approach specific to ATMPs (according to Annex I, part IV of Directive 2001/83/EC).

126 For an optimal use of these regulatory tools, applicants aiming at early access are strongly encouraged
127 to initiate dialogue with regulators as early as possible to discuss their overall development plan,
128 including their quality programme and compliance of the supply chain, to ensure there is a mutual
129 agreement on the dossier expectations and they are prepared to address any uncertainties, avoid
130 delays, enable an accelerated assessment (if applicable) and ultimately achieve a successful MAA.

131 **2. Scope**

132 The scope of this document is on medicinal products that have received PRIME designation by the
133 CHMP² and includes medicinal products containing chemical, biological and/or biotechnologically
134 derived substances and Advanced Therapy Medicinal Products (ATMPs).

² Enhanced early dialogue to facilitate accelerated access of Priority Medicines (PRIME)
(https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/enhanced-early-dialogue-facilitate-accelerated-assessment-priority-medicines-prime_en.pdf)

135 It is recognized that some of the tools described in this document may be considered on a case by case
136 basis, and prior to agreement with regulators, for other products intended for early access that address
137 an unmet medical need.

138 **3. Legal and regulatory basis**

139 This guideline should be read in conjunction with EU legislation (Annex I of Dir. 2001/83/EC and
140 2001/20/EC), which details Module 3 data requirements, and scientific guidelines and technical
141 requirements according to the EU framework, in particular:

- 142 • EudraLex- Volume 2B- Notice to Applicants
- 143 • EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines.
- 144 • EudraLex Volume 4 (Good Manufacturing Practice), Guidelines on Good Manufacturing Practice
145 specific to Advanced Therapy Medicinal Products
146 ([https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf)
147 [4/2017_11_22_guidelines_gmp_for_atmps.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf))
- 148 • ICH M7 (R1) (assessment and control of DNA reactive (mutagenic) impurities in
149 pharmaceuticals to limit potential carcinogenic risk).
- 150 • ICH Q6A (specifications: test procedures and acceptance criteria for new drug substances and
151 new drug products: chemical substances).
- 152 • ICH Q6B (specifications: test procedures and acceptance criteria for biotechnological/biological
153 products).
- 154 • ICH Q8 (R2) (Pharmaceutical development).
- 155 • ICH Q9 (Quality risk management).
- 156 • ICH Q10 (Pharmaceutical quality system).
- 157 • ICH Q11 (Development and manufacture of drug substances (chemical entities and
158 biotechnological / biological entities).
- 159 • ICH Q12 (Technical and regulatory considerations for pharmaceutical product lifecycle
160 management).
- 161 • CHMP Guideline on process validation for finished products - information and data to be
162 provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1).
- 163 • EMA Questions and answers on post approval change management protocols
164 (EMA/CHMP/CVMP/QWP/586330/2010).
- 165 • EMA Meeting Report: Joint BWP/QWP workshop with stakeholders in relation to prior
166 knowledge and its use in regulatory applications (EMA/CHMP/BWP/187162/2018).

167 *This list is not exhaustive, and other guidelines may also be of relevance.

168 **4. Scientific Tools**

169 **4.1. Introduction**

170 In the context of this document, the term 'scientific tools' refers to scientific concepts, principles or
171 technologies used for development, manufacture and quality risk management of medicinal products.
172 Examples include modelling, analytical or platform technologies.

173 Of note, during the Stakeholder workshop on support to quality development in early access
174 approaches, such as PRIME and Breakthrough Therapies¹ the term 'scientific elements' was used for
175 the term 'scientific tools'.

176 **4.2. General scientific tools**

177 **4.2.1. Prior knowledge**

178 Prior knowledge is a term used in ICH (e.g. Q8, Q10 and Q11) and EMA guidelines. A definition of this
179 term was discussed at a Joint BWP/QWP workshop with stakeholders on prior knowledge and its use in
180 regulatory applications held at EMA in 2017³ (EMA/CHMP/BWP/187162/2018). A definition was agreed
181 and published in the workshop meeting report. Prior knowledge includes company knowledge from
182 development and manufacturing experience (e.g. experience based on similar compounds, products
183 and processes) as well as reference to scientific and technical publications or application of established
184 scientific principles e.g. within chemistry.

185 The availability of prior knowledge, if demonstrated to be relevant for the product in question, could be
186 good basis for shifting the time-point for completion of certain quality studies. Prior knowledge may
187 also make some development studies redundant. If the knowledge is not related to experience with the
188 molecule in question, but based on a similar molecule, then the applicability of the knowledge to the
189 new molecule needs to be justified, and the knowledge also needs to be communicated in the dossier
190 for the new molecule in the form of a summary discussion or inclusion of supportive data. Where
191 relevant, reference to previous filings should be made, but sufficiently comprehensive information
192 should be presented in the dossier for the new molecule making it possible to determine that it is
193 representative for the product in question.

194 Prior knowledge information should be included in the CTD in the section where the product specific
195 information otherwise would be, together with argumentation on how the information is relevant.

196 Prior knowledge can also stem from "platforms", which means that, for example, similar formulation,
197 manufacturing process and/or analytical testing is used across many different molecules within a
198 group. Such groups can include monoclonal antibodies, viral vector vaccines or oligonucleotides. In
199 such cases the number of products already included in the platform and other information on the
200 extent of knowledge available, together with information on the qualification of the new molecule to
201 the platform is essential in order to assess the applicability of the platform.

202 **4.2.2. Risk assessment**

203 As indicated in ICH Q8 and Q9 risk assessment is a systematic science-based process of organizing
204 information to support a risk decision to be made within a risk management process. It consists of the

³ Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications
<https://www.ema.europa.eu/en/events/joint-biologics-working-party-quality-working-party-workshop-stakeholders-relation-prior-knowledge>

205 identification of hazards and the analysis and evaluation of risks associated with exposure to those
206 hazards. This tool is typically used as part of the pharmaceutical development to evaluate the
207 formulation and manufacturing processes to understand the impact of material attributes and process
208 parameters on product quality, define their criticality and inform the studies to be conducted. With the
209 use of the identified risk profile the applicant shall justify the extent of data available in the various
210 sections of the MAA dossier.

211 It is important to note that this process starts at the beginning of product development and matures
212 over time, as the knowledge of the product and its characteristics increases. Nonetheless, applicants,
213 using the risk-based approach, are expected to present in the application dossier the picture of the risk
214 profiles as it is at the time of MAA. The potential risk resulting from incomplete data packages at time
215 of approval is considered by Regulators in the context of the benefit-risk assessment during the MAA
216 review.

217 Although risk-based approaches may also be applicable for non-PRIME products, it is worth noting the
218 difference, i.e. that the level of residual risks that can be accepted for non-PRIME products compared
219 to PRIME products (which are intended for an unmet clinical need) may be lower (e.g. it is more likely
220 to accept a lesser degree of assurance for a life-saving product compared to a product where well-
221 documented, usable alternatives exist).

222 For further guidance on the risk-based approach specific to the development of ATMPs, please refer to
223 the dedicated EMA guideline (EMA/CAT/CPWP/686637/2011).

224 **4.3. Scientific tools related to process validation**

225 Process validation is a lifecycle activity; a continuum from early clinical product and process
226 development through to a fully mature commercial process and maintenance of the process in a state
227 of control during routine commercial production.

228 For products in an early access program, the main challenge is when sufficient data are considered to
229 be available to support approval. A departure from the traditional requirement of data from a minimum
230 of three process performance qualification (PPQ) batches can be accepted by regulators when there is
231 a strong benefit/risk of the product in question. In this regard, there are several tools (described
232 below) which can facilitate flexibility in the extent and type of process validation data required prior to
233 approval. Such approaches need to be accompanied by clear plans which outline how the process
234 validation data available support the effectiveness and reproducibility of the commercial process and
235 how process validation data, based on an appropriate protocol, will continue to be gathered in the
236 post-approval phase.

237 **4.3.1. Process validation protocols**

238 A process validation protocol, also known as a process validation scheme, is a plan describing what
239 data will be gathered and how it will be analysed (see EU GMP Annex 15 and CHMP process validation
240 guidelines). Normally it is expected that most validation activities are finished at the time of MAA but
241 even today certain validation protocols are accepted as substitutes for a final validation report.
242 Examples of such protocols (for biological products) include resin lifetime studies, introduction of new
243 cell banks, and introduction of new reference standards. For accelerated procedures it may be
244 acceptable, on a case-by-case basis and supported by a risk assessment, to defer some process
245 validation activities to the post-authorisation phase and submit protocols for the studies to be
246 performed and their acceptance criteria. The scope of validation protocols could be expanded to include
247 other validation activities, for example hold time studies, transport validation, reprocessing etc.

248 Proposals for the use of protocols in additional areas of process validation should firstly be discussed
249 with EMA. Contrary to post-approval change management protocols (PACMPs) (see section on
250 regulatory tools), process validation protocols are not followed by an implementing variation as they
251 cover aspects already described in the dossier.

252 **4.3.2. Concurrent validation**

253 Concurrent validation is defined in Annex 15 of the EU Guidelines for GMP as validation carried out in
254 exceptional circumstances, justified on the basis of a strong benefit-risk ratio for the patient, where the
255 validation protocol is executed concurrently with commercialisation of the validation batches. If
256 concurrent validation is proposed, it should be appropriately justified based on patient need, and its
257 acceptance will depend on the benefit/risk balance. The decision to carry out concurrent validation
258 must be documented in the Validation Master Plan and approved by authorised personnel including the
259 Qualified Person (QP).

260 In exceptional circumstances, concurrent validation may also be appropriate where there is a small
261 patient population, resulting in batches only being manufactured infrequently. In such cases, the
262 expected batch utilisation and approximate timeframe of future batch manufacture should be
263 described.

264 The acceptance of concurrent validation is on a case-by-case basis and will depend on the extent of
265 supportive data available. It should be supported by robust application of quality risk management.
266 Any proposal for concurrent validation should also be accompanied by a supporting protocol. The
267 protocol should therefore contain all the relevant tests and acceptance criteria which the concurrent
268 validation batch must fulfil before it can successfully pass validation and be certified by the Qualified
269 Person. In addition to the release specifications, the tests registered in the protocol should include all
270 relevant in-process controls and process parameters to support a conclusion that any given batch of
271 product will be uniform. The proposed acceptance criteria for all tests should be appropriately justified
272 and met. Prior Knowledge can also be useful for justification of the protocol parameters and
273 acceptance criteria. It is also recommended to place the concurrent process validation batches on
274 stability.

275 When concurrent validation is used, evidence should be provided to demonstrate i) that studies
276 performed for process evaluation are appropriate representations of the commercial process, and ii)
277 that the control strategy will properly verify that the process has performed as intended. It is
278 recognised that in the case of accelerated development, the level of process understanding may still be
279 evolving. Nonetheless, acceptance of a concurrent validation approach for active substances and/or
280 finished products requires sufficient process evaluation data to justify that the parameters and
281 acceptance criteria included in the protocol are suitable for concluding that the process is in a state of
282 control and that the product is uniform.

283 Where available, data from other non-PPQ batches (including clinical batches) manufactured using the
284 commercial manufacturing process can be used as supportive data to justify that the process is in a
285 state of control. Supportive process evaluation data e.g. small-scale data can also be used provided
286 that they are appropriate representations of the commercial process.

287 The number of PPQ batches to be submitted prior to licensure will depend on the data package. It is
288 generally expected that data from at least one formal process validation batch from the commercial
289 manufacturing process will be available prior to approval. In exceptional cases, it may be acceptable
290 not to have successfully manufactured any PPQ batches prior to approval. This will have to be
291 supported by a comprehensive risk-based approach and will depend on the extent of Prior Knowledge

292 which can be leveraged and other supporting validation data from non-PPQ batches or small scale
293 batches. Provision of interim process validation data during MAA review is also desirable.

294 A concurrent validation approach may have implications for the timing and scope of GMP inspections.
295 Concurrent validation proposals should therefore be discussed pre-submission with the relevant EU
296 supervisory authority.

297 For products where process validation data would normally be required prior to approval (e.g.
298 biological products, chemical products manufactured using non-standard processes), the data from the
299 concurrent process validation batches should be submitted post-approval. However, formal regulatory
300 approval will generally not be required for release of concurrent validation batches to the market.
301 However, depending on the benefit-risk ratio evaluation, formal regulatory approval could be required
302 for release of concurrent validation batches to the market. Several mechanisms exist to request the
303 submission of the post-approval process validation data, for example a Recommendation, a Specific
304 Annex II condition to the Commission Decision for a Conditional Marketing Authorisation). The most
305 appropriate mechanism will be decided case-by-case and will depend on the overall data package and
306 level of risk.

307 **4.3.3. Deferral of the submission of certain process validation data**

308 Aside from concurrent validation, it may be possible under certain circumstances to defer certain
309 process validation activities to the post-approval phase. This would allow for a mixed approach where
310 some process validation data are available prior to authorisation and other data is provided post-
311 approval. To manage the provision of additional data post approval, regulatory tools (e.g.
312 recommendations, protocols, variations (see section on regulatory tools) will be agreed by Regulators
313 and Applicants.

314 **4.3.4. Decoupling active substance and finished product process 315 validation**

316 In order to avoid delays in finished product PPQ activities, it may be acceptable, under certain
317 circumstances, to manufacture finished product PPQ batches using active substance batches which
318 were produced prior to formal active substance process validation, provided the active substance
319 batches were manufactured under GMP. If this approach is chosen, it should be demonstrated that
320 such active substance batches are sufficiently representative of the commercial manufacturing process
321 and will meet their intended specifications for quality and purity.

322 **4.3.5. Continuous process verification**

323 Continuous process verification is an alternative approach to traditional process validation in which
324 manufacturing process performance is continuously monitored and evaluated (ICH Q8). Continuous
325 process verification can be used in addition to, or instead of, traditional process validation (ref. CHMP
326 guideline on process validation for finished products EMA/CHMP/CVMP/QWP/BWP/70278/2012-
327 Rev1,Corr.1).

328 When there is extensive prior knowledge on a particular manufacturing process and it comprises
329 extensive in-line, on-line or at-line controls, continuous process verification could be used to validate
330 the manufacturing process and facilitate early access since the robustness of the manufacturing
331 process can be demonstrated in the dossier by a discussion on the appropriateness and feasibility of
332 the continuous process verification strategy in the development section, supported with data from at
333 least laboratory or pilot scale batches, and a continuous process verification scheme in 3.2.R. Actual

334 data generated during continuous process verification at production scale should be available at the
335 site for inspection.

336 **4.4. Scientific tools related to control strategy**

337 **4.4.1. Initial filing with a more “constrained” control strategy**

338 As articulated by ICH Q8 to Q11, the more knowledge an applicant has of their product and process,
339 the more flexibility can be afforded in the approved control strategy. For products undergoing an
340 accelerated development timeline, product and process knowledge (e.g., uncertainty on the criticality
341 of attributes, their control by the manufacturing process, and analytical capability) may still be
342 evolving at the time of filing. Thus, the amount of data available to support its control strategy at the
343 time of approval may be reduced compared to a product undergoing a standard development. In order
344 to facilitate faster access for patients, some process development and evaluation studies could be
345 deferred to the post-approval phase, depending on the benefit/risk balance. In order to support the
346 deferral of such data, applicants may choose to file with a more constrained control strategy. Such a
347 constrained control strategy could encompass some or all of the following elements:

- 348 • Additional specification tests
- 349 • Additional in-process controls
- 350 • Additional process parameters
- 351 • A higher number of critical process parameters
- 352 • Narrower ranges for critical process parameters (CPPs)

353 Applicants should justify how the tighter control of the manufacturing process supports the deferral of
354 some process development and evaluation studies. For example, in the case where process evaluation
355 studies to demonstrate clearance of a certain impurity are not available at the time of registration, a
356 release test or IPC could be registered until those studies are complete and support discontinuation of
357 routine testing. As another example, during a standard development timeline, data from small-scale
358 process evaluation studies may be used to justify the classification of a process parameter as non-
359 critical. Where such process evaluation studies are still ongoing, some process parameters could
360 default to critical until the data is available post-approval to support their downgrading. Ranges of
361 process parameters could also be narrowed until data is available showing that a wider range of
362 process parameter inputs does not impact the relevant critical quality attributes (CQAs) outputs of that
363 manufacturing step.

364 Once suitable data has been gathered post-approval, an appropriate variation could be submitted to
365 “relax” or de-constrain the control strategy e.g. downgrade/remove process parameters, widen ranges
366 etc. The process evaluation data required to support the relaxing of a control strategy could be agreed
367 during the initial assessment phase as part of a PACMP.

368 When planning the timing of process development and process evaluation work, the major
369 consideration of which (if any) process development studies could be deferred should be that the
370 safety and efficacy of the product must still be assured at the time of approval.

371 **4.4.2. The acceptance and use of *in-silico* models and purge factor** 372 **calculations.**

373 A control strategy that is based on product and process understanding and utilisation of risk
374 management principles will lead to a combination of process design and control and appropriate

375 analytical testing, which can also provide an opportunity to shift controls upstream and minimize the
376 need for end-product testing.

377 ICH M7 foresees the use of in-silico models in the control of mutagenic impurities and defines four
378 potential approaches to the development of a control strategy (section 8.1), where option 4 relies on
379 understanding of process parameters and impact on residual impurity levels (including fate and purge
380 knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below
381 the acceptable limit such that no analytical testing is recommended for this impurity. (i.e., the impurity
382 does not need to be listed on any specification).

383 The risk assessment can in this case be based on knowledge of physicochemical properties and process
384 factors that can influence the fate and purge of the impurity. Where justification based on scientific
385 principles alone is not considered sufficient, analytical data to support the control approach is
386 expected.

387 It is important to demonstrate that the fate of impurities/purge argument for the impurity is robust
388 and will consistently assure a negligible probability of an impurity residing in the final drug substance
389 above the acceptable limit.

390 In addition, for Lifecycle Management purposes section 8.5 of ICH M7 also states that in some cases,
391 the use of statistical process control and trending of process measurements can be useful for continued
392 suitability and capability of processes to provide adequate control on the impurity. Statistical process
393 control can be based on process parameters that influence impurity formation or clearance, even when
394 that impurity is not routinely monitored.

395 From these excerpts from ICH M7 it can be seen that in-silico calculations of carry-over of genotoxic
396 impurities can be justified, where it has been shown that carry-over and purge calculations are based
397 on physicochemical parameters. The physicochemical parameters in themselves may be collected both
398 from calculations and measured data from experiments.

399 However, in many cases the programs and algorithms used by Applicants for carry-over calculations
400 have not been fully transparent to the Authorities, in some cases hampering the assessment and
401 acceptability of in-silico purge calculations.

402 In order to address this, topics that may be of interest for further discussions include:

- 403 • Discussion on what parameters of purge calculations should be/can be transparent in an MAA
- 404 • Insight into the software used for purge calculations from side of the Authorities
- 405 • Possibility of mutually recognised software for purge calculations
- 406 • Follow-up on regulatory issues that may follow from the use of such calculations, e.g. how to
- 407 handle a database that changes over time as more data is added/or removed (evolving
- 408 databases)

409 **4.4.3. Front-loading of control strategy activities/ CMC development plan**

410 In accelerated development programs, development of a robust control strategy may be on a critical
411 path. By front-loading of process development activities, a more robust quality data package may be
412 available to support the control strategy at the time of MAA approval. This could include early planning
413 of small-scale studies required to establish process parameter ranges and conducting risk assessment
414 activities to identify and mitigate gaps in process development and evaluation.

415 **4.5. Approaches related to GMP compliance**

416 **4.5.1 Launching from an investigational medicinal product site**

417 According to the European legislation, all medicinal products for human use manufactured or imported
418 into the Union, including investigational medicinal product (IMP) and medicinal products intended for
419 export, should be manufactured in accordance with principles and guidelines of good manufacturing
420 practice (GMP). In addition, according to Article 40 of Directive 2001/83/EC and Article 13 of Directive
421 2001/20/EC (as amended), the manufacturers of these medicinal products are subject to the holding of
422 an authorisation, covering marketed or investigational medicinal products.

423 In certain cases, to facilitate timely patient access to medicines that address unmet medical needs, the
424 Agency could allow at the time of submission of the dossier, an investigational product manufacturing
425 authorisation holder as the site of manufacture. A commercial manufacturing authorisation issued
426 under Article 40 of Directive 2001/83 confirming that the IMP manufacturer is authorised to
427 manufacture marketed products will be required at the time of the Opinion of the MA. Therefore, the
428 applicant should ensure that the necessary application for the relevant MIA is submitted to the relevant
429 supervisory authority in time to allow inspection prior to the grant the Opinion, otherwise the CHMP will
430 ask the supervisory authority to carry out an inspection and the application will be delayed until the
431 MIA has been granted. In such circumstances, evidence that an adequate level of compliance to GMP
432 to manufacture marketed products is in place, that an effective Pharmaceutical Quality System has
433 been implemented , and that manufacturing and supply processes have been designed and validated
434 using robust and efficient Quality Risk Management prior to certification and release of the marketed
435 batches. The use of a Comparability Assessment exercise (See 4.6) could be considered and applied for
436 the evaluation of GMP gaps to support the certification and release of the marketed batches. In the
437 case the manufacturing site authorised under the Article 13 of Directive 2001/20/EC will not be the site
438 will perform final batch release of any marketed batches, the Qualified Person of the MIA holder
439 authorised under Article 40 of Directive 2001/83 should be involved into the evaluation of the level of
440 GMP compliance.

441 **4.5.2 Alignment of quality review and GMP inspections**

442 During the granting of a marketing authorisation (MA), a GMP inspection could be required in order to
443 assess the GMP compliance of a site. Submission of the supply chain information in advance of the
444 submission is necessary to evaluate, the need for a GMP inspection and to co-ordinate any requested
445 inspection within the assessment procedure.

446 During accelerated timelines, it is important to ensure the quality review and GMP inspection activities
447 are aligned and appropriate mechanisms to share knowledge and information obtained through
448 inspection or assessment activities are utilised by the Agency to facilitate the evaluation of a MAA.

449 **4.5.3 Use of biological starting material manufactured under a lower level 450 of GMP**

451 The establishment of new seed/cell lots/banks and viral seed stocks should be done in accordance with
452 the guidelines and principles of GMP (refer to Annex 2 or Part IV GMP for ATMPs). The level of GMP
453 increases in detail from early to later steps in the manufacture of biological active substances but GMP
454 principles should always be adhered to. Under exceptional conditions, it could be acceptable to use
455 starting material (e.g. MCB) that may be considered by the applicant to have been manufactured
456 under a lower level of GMP, provided documentation is available to confirm traceability, and prevention
457 of contamination, including information related to components used during development with potential
458 impact on product safety, and that an extensive characterisation and testing have been carried out. A

459 documented risk assessment should be conducted to identify the testing requirements necessary to
460 ensure the quality of the starting material and the medicinal product. Sufficient documentation should
461 be available on the production of the starting material and also a comprehensive viral safety study
462 complying to GMP should be performed. The competent authorities will evaluate the risk assessment
463 and should agree to the proposed strategy in the context of the assessment of the marketing
464 authorisation application/clinical trial authorisation application.

465 **4.6. Scientific tools related to stability**

466 In accelerated development programs, standard stability data packages may not be feasible and
467 alternative paths may be needed while still assuring the stability of the product.

468 **4.6.1. Stability models generated from stability of structurally similar** 469 **molecules (Biotech)**

470 In accordance with ICH Q5C stability data fully covering the period of the claimed shelf life is requested
471 for biological products which could delay the MA approval of PRIME products with accelerated
472 development. For a biologic PRIME product, trends in stability data, and therefore the claimed shelf
473 life, could be extrapolated using predictive stability models generated from prior knowledge of the
474 stability of structurally similar molecules. In such cases, it may be possible to approve a shelf life which
475 is longer than the available product-specific real time stability data. Success of this type of approach
476 requires evaluation and justification that the risks in extrapolation of stability data are appropriately
477 mitigated by sufficient prior knowledge of the stability of similar products and commitments to report
478 deviations from the expected stability trends and out of specification results.

479 The data used to generate the predictive stability model should be provided in the dossier. The types
480 of products from which the model was derived should be described. In order to justify the use of a
481 predictive stability model, the Company should provide a rationale for any statistical analyses used and
482 for the parameters used to show that the current product fits the model generated using data from
483 other products. Data from stress studies could be submitted to further support the shelf life.

484 The trend in the stability model is considered of greater importance than the actual levels of
485 degradation seen in different products. The trends should then be applied to what could be claimed as
486 clinically qualified levels for each quality attribute for the PRIME product and the release requirements
487 back-calculated from the level observed at the intended shelf-life.

488 In cases where the data for the new product fits the model, while considering the change over the
489 proposed shelf life, it should be possible to set release acceptance criteria which would assure that the
490 clinically relevant quality attribute limits are met at the end of shelf life. As real time stability data are
491 generated post-approval, the company should verify on a continuous basis that the stability of the
492 product continues to fit the predictions of the model. This should be supported by commitments to
493 report deviating trends, out of specification (OOS) results etc., and what actions will be taken in case
494 the results no longer fit the model.

495 There are situations where the models do not fit. It is important to find out why and apply this
496 knowledge to new products in order to decide early on if the model would fit or not.

497 It may be possible to leverage data from other presentations when establishing the shelf life. For
498 example, using stability data from a vial presentation to establish the shelf life for a pre-filled syringe
499 presentation. For such approaches it should be demonstrated that the results from different
500 presentations show similar trends, this information can then be included in the model and extrapolated

501 to the intended commercial presentation. There should be no major changes to the production apart
502 from the container closure system.

503 It is acknowledged that the principles will be difficult to apply to other groups of products than those
504 used to establish the model (i.e. a model based on monoclonal antibodies is unlikely to apply in
505 general to other types of recombinant products). The generation of a predictive stability model and its
506 application should be agreed in advance with the agency.

507 **4.6.2. Stability based on supportive knowledge (small molecules)**

508 It is acknowledged that in some cases general prior knowledge of the stability of an active substance
509 can be gained from similar molecules e.g. within the same class, considerations of functional groups in
510 the molecule and the relevant environment regarding e.g. pH and moisture. Prior knowledge may also
511 be available on the stability of products containing similar molecules. Knowledge can also be gained
512 from the use of accelerated stability using more challenging conditions of temperature and humidity,
513 and modelling of the results. With regards to predictions of chemical stability these accelerated
514 stability approaches are well established.

515 This prior knowledge or results from modelling could be used as supportive information to claim a re-
516 test period beyond the time-point justified by the results from long-term studies and extrapolation as
517 per ICH Q1E. In this case, a commitment to inform the regulators immediately if the stability of the
518 active substance/medicinal product is not as anticipated and restrict the retest period/shelf life
519 accordingly should be provided. This should be accompanied by a second commitment to submit the
520 remaining quality data which would otherwise generally required (e.g. at least 12 months under long
521 term storage and maximum 12 month extrapolation) when available, if not otherwise agreed with the
522 agency.

523 Regardless of the approach taken, regular ICH studies should be run in parallel and additional stability
524 commitments provided, as described in ICH Q1A.

525 In justified cases, it may be acceptable not to define a re-test period for an active substance, and
526 instead test it before use. This could be relevant if a constrained control strategy is used, or if other
527 supportive knowledge is available.

528 **4.7. Scientific tools related to comparability (biologicals)**

529 A risk-based approach, such as the one developed for ATMPs⁴, can potentially be used to tailor the
530 comparability study by identifying CQAs impacted by manufacturing changes. This will allow for a
531 reduced comparability package focusing only on the relevant CQAs. Based on this, a justified set of
532 release, (accelerated) stability and/or characterization data can be used to demonstrate comparability.

533 The following aspects are taken into account.

534 **4.7.1. Using prior knowledge to tailor comparability studies**

535 Prior knowledge based on e.g. the same platform or from similar products can be used to predict the
536 impact of specific manufacturing changes. A risk-based approach could potentially be applied to tailor
537 the comparability study by identifying CQAs most likely to be impacted by manufacturing changes. This
538 could allow a company to justify proportionate requirements on the comparability data.

⁴ The risk-based approach for ATMP is an established regulatory tool that permits adaptation of the data in MAA to the specific risks of the product.

539 The applicability of prior knowledge on which the choice of quality attributes to be studied in the
540 comparability exercise should be justified by the representativeness of the data for the product in
541 question. After the initial comparability studies an analysis of the need for additional studies should be
542 performed taking into account the residual uncertainties from the initial comparability studies, before
543 the final comparability exercise can be submitted.

544 **4.7.2. Risk based identification of CQAs**

545 Comparability studies are expected to be comprehensive. (ICH Q5E states: *Generally, quality data on*
546 *the pre- and post-change product are generated, and a comparison is performed that integrates and*
547 *evaluates all data collected, e.g., routine batch analyses, in-process control, process*
548 *validation/evaluation data, characterisation and stability, if appropriate).*

549 However, in case of development of medicines for early access it could be justified to have a less
550 comprehensive comparability exercise limited to identified relevant Critical Quality attributes (CQAs). A
551 risk-based strategy is used to identify and select CQAs. CQAs are identified in a risk assessment by
552 evaluating for each of the qualitative or quantitative characteristics whether and to what extent it could
553 potentially contribute to the efficacy or a specific safety risk of the product. Then, as a second step,
554 considering the type of the change introduced (e.g. change to process step) and the available prior
555 knowledge, the potential impact of such change to each CQA is considered. Based on that risk
556 assessment the comparability study could be limited to a justified set of CQA.

557 A risk-based approach also takes into account the type of change made to the manufacturing process
558 and how this relates to the prior knowledge used to predict and select the relevant impacted CQAs.

559 Other considerations include whether the analytical methods are capable of detecting changes in the
560 quality attributes and whether there are any other relevant data that could support the comparability
561 exercise, such as small-scale data.

562 **4.7.3. Separate assessment of individual changes**

563 In case multiple changes are introduced there are two possible scenarios: either all the changes are
564 introduced at the same time, or each change (or combination of some changes) is introduced in
565 different stages of development of the manufacturing process.

566 In the case of introduction of all changes at the same time, it is generally expected that comparability
567 will be demonstrated for the combined introduction of these changes. However, separate assessment
568 of individual changes could be acceptable when it is justified that the impact is independent for each of
569 the different changes (i.e. there are no interactions). The acceptability of separate comparability data
570 should be duly justified (dependent on the type of change, type of manufacturing process and type of
571 product).

572 In case of sequential introduction of the changes to the manufacturing process at different stages of
573 development, it is generally acceptable to provide serial (sequential) comparability data,
574 demonstrating comparability between each of the development stages.

575 Depending on the change made it may not be necessary to assess its impact all the way to the finished
576 product. It may be sufficient the assess of the impact on a particular step of a limited number of steps,
577 by demonstrating comparability for a relevant intermediate after modified manufacturing step(s).

578 For any scenario, the comparability between the product used for the clinical trials and the commercial
579 process has to be fully justified.

580 **4.7.4. Statistical tools for comparability**

581 Statistics may provide useful information to support comparability even though any statistical approach
582 has its own limitations and strengths. Those limitations should be well understood and documented
583 before conduct of the comparability exercise and in order to make informed decisions on the
584 comparability utilizing the statistical results.

585 In any case, it is essential that an appropriate pre-specified plan with a justification for the statistical
586 approach chosen and the comparability acceptance criteria proposed for the relevant quality attribute
587 selected according to a risk-based approach is provided in the regulatory submission.

588 Inclusion of side-by-side analysis of individual values with accompanying descriptive statistics to
589 summarize data (e.g. min-max and 3*sigma ranges) is recommended, particularly when comparing a
590 limited number of samples/batches. Likewise, suitable graphical representations (e.g., individual values
591 scattergrams) could be provided, allowing the identification of possible shifts within the acceptance
592 criteria.

593 In case there are only very few batches available (sometimes in combination with large variability e.g.
594 autologous cell products) a statistical tool may not be useful to demonstrate comparability, in such
595 cases a comparison with historic ranges may be the best approach.

596 Further consideration could also be given to the draft CHMP reflection paper on statistical methodology
597 for the comparative assessment of quality attributes (EMA/CHMP/138502/2017) and the meeting
598 report "Workshop on the reflection paper on statistical methodology for the comparative assessment of
599 quality attributes in drug development" (EMA/CHMP/579441/2018).

600 **4.7.5. Comparability and Stability**

601 In general, full real time stability studies are not required to support comparability. Nevertheless,
602 stability data can be relevant to understand the impact of manufacturing changes. In this regard, it is
603 more reasonable to focus on dedicated stability studies under accelerated or stress conditions that can
604 be of value to identify possible differences. Such pre/post-change comparability stability studies done
605 using relevant accelerated conditions on representative material could also be acceptable to support a
606 shelf life claim based on pre-change or platform real time stability data.

607 **4.7.6. Comparability for ATMPs**

608 ATMPs in general are characterized by starting materials of inherent variability (for cell/tissue-based
609 products), complex biological features and manufacturing processes. Therefore, ATMPs are outside the
610 scope of the ICH Q5E guideline and a specific Q&A document is available: Comparability considerations
611 for Advanced Therapy Medicinal Products (ATMP)- EMA/CAT/499821/2019.

612 The Q&A document should be read in conjunction with this Toolbox document.

613 **4.7.7. Need for additional (non)clinical data**

614 In case full comparability of the CQAs related to safety and efficacy cannot be demonstrated, additional
615 (non) clinical data may be needed before approval of the MAA. In exceptional cases, based on a risk-
616 benefit assessment, these could be post-approval clinical studies.

617 **5. Regulatory tools**

618 **5.1. Introduction**

619 EMA is committed to enabling early patient access to new medicines, particularly those that target an
620 unmet medical need or are of major public health interest. The Agency seeks to support the medicine
621 development process from an early stage and to offer regulatory mechanisms to help promising new
622 medicines reach patients as early as possible, without compromising their quality, safety and efficacy.
623 In this context, the Agency EMA has different procedures available to establish an early dialogue with
624 regulators and support prospective planning. These include:

625 a) **scientific advice/protocol assistance** during development, whereby the EMA provides medicine
626 developers advice on the most appropriate way to generate robust evidence on a medicine's benefits
627 and risks. This supports the timely and sound development of high-quality, effective and safe
628 medicines, for the benefit of patients. Scientific advices are particularly suitable to agree with the EMA
629 on tailored development approaches such as filing with an initial more restricted control strategy,
630 concurrent validation approaches, prior knowledge etc.

631 Applicants can also request a parallel scientific advice or a consultative advice with EMA and US FDA to
632 optimize product development and avoid unnecessary testing replication or unnecessary diverse
633 testing methodologies in both regions. The agencies conduct this procedure under the auspices of the
634 confidentiality arrangement between the European Commission, the EMA, and FDA.

635 Further information can be found on the dedicated EMA website (references below).

636 b) **pre-submission meetings between applicants and the EMA/(Co-) Rapporteurs.** The
637 meetings should take place approximately 7 months prior to the anticipated date of submission of the
638 application. They are a vital opportunity for applicants to obtain procedural, regulatory and legal advice
639 from the EMA and the Rapporteurs, and discuss issues specific to their upcoming application. The EMA
640 product team is available to address any questions MAHs may have regarding their MAA. Further
641 information can be found on the European Medicines Agency pre-authorisation procedural advice for
642 users of the centralised procedure (EMA/24037/2019) (references below).

643 In addition, the EU regulatory framework contains a number of regulatory tools or strategies that can
644 be used and adapted to facilitate timely patient access to medicines that address unmet medical
645 needs.

646 The available regulatory tools are further detailed below.

647 **5.2. Regulatory tool 1: accelerated assessment**

648 The accelerated assessment is a procedure reserved to medicinal products of major therapeutic
649 interest (recital 33 and Article 14(9) of Regulation (EC) No 726/2004). Relevant information on the
650 eligibility criteria, applicable evaluation timelines, procedure to apply for an accelerated assessment
651 can be found on the dedicated EMA webpage (see references below).

652 This procedure is intended to shorten the active review time of a MAA from 210 to 150 days and
653 therefore to potentially secure an earlier access of the medicine to patients. In order to achieve this,
654 applicants should aim at filing a complete MA dossier and avoid the submission of data during the
655 review, to avoid the timetable is reverted to normal due to major objections raised during the
656 evaluation (e.g. major objections include concerns related to an insufficient control strategy,

657 redefinition of active substance starting materials, comparability between clinical material and
658 commercial product not fully demonstrated).

659 Applicants are encouraged to discuss proactively with regulators their intention to apply for accelerated
660 assessment and any issues related to the dossier, and follow any scientific advice received, to ensure
661 appropriateness of an accelerated assessment procedure and a possible way forward to address any
662 potential obstacles. Adequate planning regarding manufacturing authorisation requirements, GMP
663 compliance and any potential GMP inspection should also be taken into consideration to prevent delays
664 (see GMP section). Applicants should ensure that manufacturing sites are inspection ready at the time
665 of submission of the application.

666 **5.3. Regulatory tool 2: conditional marketing authorisation (CMA)**

667 This is a tool available for medicinal products aiming at the treatment, prevention or medical diagnosis
668 of seriously debilitating or life-threatening diseases, or medicinal products to be used in emergency
669 situations in response to public health threats. In this case, a marketing authorisation may be granted
670 prior to the submission of comprehensive clinical data provided that the benefit-risk balance of the
671 product is considered positive and the benefits of immediate availability outweighs the risk of less
672 comprehensive data than normally required, i.e. the medicines is able to address an unmet medical
673 need. Such conditional marketing authorisations are subject to specific obligations, aiming at
674 generating the missing data and confirming the favourable benefit-risk profile.

675 Conditional marketing authorisations should be restricted to situations where only the clinical part of
676 the application dossier is less complete than normal. Incomplete pre-clinical or pharmaceutical data
677 should be accepted only in the case of a product to be used in emergency situations, in response to
678 public health threats.

679 Conditional marketing authorisations are valid for one year and can be renewed annually. During this
680 period, the holder will be required to complete these specific obligations (ongoing or new studies, and
681 in some cases additional activities) with a view to providing comprehensive data to address
682 uncertainties and confirming that the benefit-risk balance is positive.

683 The legal basis for conditional marketing authorisation is Article 14-a of Regulation (EC) 726/2004 as
684 further defined in Commission Regulation EC No 507/2006 and information on the requirements to be
685 met and application process are described in the CHMP guideline on the scientific application and
686 practical arrangements on the CMA (EMA/CHMP/509951/2006, Rev.1) and the dedicated EMA webpage
687 (see references below).

688 **5.4. Other regulatory tools:**

689 **Post-approval change management protocols (PACMPs)**

690 The concept of PACMP was introduced in the EU through the Commission's Guideline on the details of
691 the various categories of variations to the terms of marketing authorisations for medicinal products for
692 human use and veterinary medicinal products (2010/C 17/01) that supports the Variations Regulation
693 (Commission Regulation (EC) No 1234/2008).

694 A PACMP enables a stepwise approach in the assessment of changes. The protocol would describe the
695 specific changes that a company would like to implement during the lifecycle of the product (e.g. to
696 add a new manufacturing site, to upscale a manufacturing process) and how these would be prepared
697 and verified. The results from the pre-defined studies would be submitted post-approval through a

698 variation to implement the change. This approach enables an early assessment of the strategy to be
699 pursued, thereby lowering the reporting category of the implementing variation, which in turn reduces
700 the overall regulatory review and implementation time (ref. EMA Q&A on PACMP-
701 EMA/CHMP/CVMP/QWP/586330/2010).

702 **Post-authorisation measures (PAMs)**

703 The intention of PAMs is per se not to facilitate early access or facilitate deferral of data generation.
704 PAMs are means for regulators to request any additional data that from a public health perspective, are
705 needed to complement the available data. These can be categorized as specific obligation [SOB],
706 annex II condition [ANX], additional pharmacovigilance activity in the risk-management plan (RMP)
707 [MEA] or recommendation [REC].

708 The existence of these PAMs does not aim at promoting premature approvals of marketing
709 authorisations or post-authorisation procedures. The background and rationale for requesting PAMs will
710 be described in the relevant assessment, which will present the context and nature of the PAM. Based
711 on the assessment of the committee(s), PAMs are classified into their appropriate legal framework
712 under which they will be enforced.

713 The PAM selected depends on the criticality of the data set/measure in relation to the clinical use of the
714 product and its impact on the benefit/risk. For example, a recommendation may be issued to further
715 consider the implementation of a more sensitive analytical method for characterisation or batch release
716 purposes; or to review and, if necessary, revise product specifications once more batch data become
717 available.

718 *While not a regulatory tool, it is acknowledged that in certain cases some data generation to support
719 approval may be on-going at the time of MAA (e.g. stability, process validation studies) and applicants
720 may submit the missing data as part of the responses to the list of questions or list of outstanding
721 issues. When this situation is foreseen applicants are encouraged to discuss this approach upfront with
722 regulators and seek agreement to ensure there is a mutual understanding.

723 **References**

- 724 • Annex I of Dir. 2001/83/EC
- 725 • EudraLex- Volume 2B- Notice to Applicants
- 726 • EudraLex Volume 4 (Good Manufacturing Practice), Guidelines on Good Manufacturing Practice
- 727 • ICH M7 (R1) (assessment and control of DNA reactive (mutagenic) impurities in
728 pharmaceuticals to limit potential carcinogenic risk)
- 729 • ICH Q1A Stability testing of new drug substances and drug products
- 730 • ICH Q1E note for guidance on evaluation of stability data
- 731 • ICH Q5C Stability testing of biotechnological/biological products
- 732 • ICH Q6A (specifications: test procedures and acceptance criteria for new drug substances and
733 new drug products: chemical substances).
- 734 • ICH Q6B (specifications: test procedures and acceptance criteria for biotechnological/biological
735 products).
- 736 • ICH Q8 (R2) (Pharmaceutical development).

- 737 • ICH Q9 (Quality risk management).
- 738 • ICH Q10 (Pharmaceutical quality system).
- 739 • ICH Q11 (Development and manufacture of drug substances (chemical entities and
740 biotechnological / biological entities).
- 741 • ICH Q12 (Technical and regulatory considerations for pharmaceutical product lifecycle
742 management).
- 743 • CHMP Guideline on process validation for finished products - information and data to be
744 provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1).
745 [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-process-validation-
746 finished-products-information-data-be-provided-regulatory-submissions_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-process-validation-finished-products-information-data-be-provided-regulatory-submissions_en.pdf)
- 747 • CHMP Guideline on process validation for the manufacture of biotechnology-derived active
748 substances and data to be provided in the regulatory submission
749 (EMA/CHMP/BWP/187338/2014) [https://www.ema.europa.eu/en/documents/scientific-
750 guideline/guideline-process-validation-manufacture-biotechnology-derived-active-substances-
751 data-be-provided_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-process-validation-manufacture-biotechnology-derived-active-substances-data-be-provided_en.pdf)
- 752 • Guideline on the risk-based approach according to Annex I, part IV of Dir 2001/83/EC applied
753 to Advanced Therapy Medicinal Products (EMA/CAT/CPWP/686637/2011).
754 [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-based-approach-
755 according-annex-i-part-iv-directive-2001/83/ec-applied-advanced-therapy-medicinal-
756 products_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-based-approach-according-annex-i-part-iv-directive-2001/83/ec-applied-advanced-therapy-medicinal-products_en.pdf)
- 757 • CHMP Q&A on Comparability considerations for Advanced Therapy Medicinal Products (ATMP)
758 (EMA/CAT/499821/2019) [https://www.ema.europa.eu/en/documents/other/questions-
759 answers-comparability-considerations-advanced-therapy-medicinal-products-atmp_en.pdf](https://www.ema.europa.eu/en/documents/other/questions-answers-comparability-considerations-advanced-therapy-medicinal-products-atmp_en.pdf)
- 760 • Draft Reflection paper on statistical methodology for the comparative assessment of quality
761 attributes in drug development (EMA/138502/2017).
762 [https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-
763 statistical-methodology-comparative-assessment-quality-attributes-drug_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-statistical-methodology-comparative-assessment-quality-attributes-drug_en.pdf)
- 764 • CHMP Guideline on the scientific application and the practical arrangements necessary to
765 implement Commission Regulation (EC) No 507/2006 on the conditional marketing
766 authorisation for medicinal products for human use falling within the scope of Regulation (EC)
767 No 726/2004 (EMA/CHMP/509951/2006, Rev.1)
768 [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-
769 practical-arrangements-necessary-implement-commission-regulation-ec/2006-conditional-
770 marketing-authorisation-medicinal-products-human-use-falling_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-commission-regulation-ec/2006-conditional-marketing-authorisation-medicinal-products-human-use-falling_en.pdf)
- 771 • EMA Meeting Report: Workshop with stakeholders on support to quality development in early
772 access approaches (i.e. PRIME, Breakthrough Therapies)
773 (EMA/CHMP/BWP/812924/2018). [https://www.ema.europa.eu/en/documents/report/report-
774 workshop-stakeholders-support-quality-development-early-access-approaches-ie-prime_en.pdf](https://www.ema.europa.eu/en/documents/report/report-workshop-stakeholders-support-quality-development-early-access-approaches-ie-prime_en.pdf)
- 775 • EMA Meeting Report: Joint BWP/QWP workshop with stakeholders in relation to prior
776 knowledge and its use in regulatory applications (EMA/CHMP/BWP/187162/2018).
777 [https://www.ema.europa.eu/en/documents/report/meeting-report-joint-biologics-working-
778 party/quality-working-party-workshop-stakeholders-relation-prior-knowledge-its-use-
779 regulatory-applications_en.pdf](https://www.ema.europa.eu/en/documents/report/meeting-report-joint-biologics-working-party-quality-working-party-workshop-stakeholders-relation-prior-knowledge-its-use-regulatory-applications_en.pdf)

- 780 • EMA Meeting Report: Workshop on the reflection paper on statistical methodology for the
781 comparative assessment of quality attributes in drug development”
782 (EMA/CHMP/579441/2018). [https://www.ema.europa.eu/en/documents/report/meeting-](https://www.ema.europa.eu/en/documents/report/meeting-report-workshop-draft-reflection-paper-statistical-methodology-comparative-assessment/chmp/138502/2017_.pdf)
783 [report-workshop-draft-reflection-paper-statistical-methodology-comparative-](https://www.ema.europa.eu/en/documents/report/meeting-report-workshop-draft-reflection-paper-statistical-methodology-comparative-assessment/chmp/138502/2017_.pdf)
784 [assessment/chmp/138502/2017_.pdf](https://www.ema.europa.eu/en/documents/report/meeting-report-workshop-draft-reflection-paper-statistical-methodology-comparative-assessment/chmp/138502/2017_.pdf)
- 785 • EMA PRIME: priority medicines: [https://www.ema.europa.eu/en/human-regulatory/research-](https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines)
786 [development/prime-priority-medicines](https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines)
- 787 • EMA webpage on accelerated assessment: [https://www.ema.europa.eu/en/human-](https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment)
788 [regulatory/marketing-authorisation/accelerated-assessment](https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment)
- 789 • EMA webpage on conditional marketing authorisation: [https://www.ema.europa.eu/en/human-](https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation)
790 [regulatory/marketing-authorisation/conditional-marketing-authorisation](https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation)
- 791 • EMA Questions and answers on post approval change management protocols
792 (EMA/CHMP/CVMP/QWP/586330/2010). [https://www.ema.europa.eu/en/documents/scientific-](https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-post-approval-change-management-protocols_en.pdf)
793 [guideline/questions-answers-post-approval-change-management-protocols_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-post-approval-change-management-protocols_en.pdf)
- 794 • EMA Post-authorisation measures: questions and answers.
795 [https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-measures-questions-answers)
796 [measures-questions-answers](https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-measures-questions-answers)
- 797 • EMA Scientific advice and protocol assistance: [https://www.ema.europa.eu/en/human-](https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance)
798 [regulatory/research-development/scientific-advice-protocol-assistance](https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance)
- 799 • European Medicines Agency pre-authorisation procedural advice for users of the centralised
800 procedure: [https://www.ema.europa.eu/en/documents/regulatory-procedural-](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en-0.pdf)
801 [guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en-0.pdf)
802 [procedure_en-0.pdf](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en-0.pdf)
- 803 • EMA Guidance on meetings with applicants on the responses to questions received from EMA
804 Scientific Committees during the evaluation within the centralised procedure
805 (EMA/636600/2014). [https://www.ema.europa.eu/en/documents/regulatory-procedural-](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-meetings-applicants-responses-questions-received-european-medicines-agency-scientific_en.pdf)
806 [guideline/guidance-meetings-applicants-responses-questions-received-european-medicines-](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-meetings-applicants-responses-questions-received-european-medicines-agency-scientific_en.pdf)
807 [agency-scientific_en.pdf](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-meetings-applicants-responses-questions-received-european-medicines-agency-scientific_en.pdf)