

Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products

Draft

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28 **1. Introduction**

29 There has been significant interest in developing drug delivery technologies to achieve
30 improved delivery of poorly soluble, high-toxic and/or unstable drugs, to increase
31 tissue targeting and/or to improve the efficiency of cytosolic delivery of
32 macromolecular drugs. One of the strategies under development uses block copolymer
33 micelles. Block copolymer micelles are self-assembled micelles, and they are typically
34 prepared from AB block copolymers. Other more complex compositions have been
35 proposed. An active substance can be incorporated into the inner core of the block
36 copolymer micelle product by chemical conjugation or by physical entrapment. Block
37 copolymers with amphiphilic character spontaneously assemble into polymeric micelles
38 in aqueous media, hydrophobic interactions typically drive this self-association.
39 However, other driving forces may be used to promote micelle formation and enhance
40 micelle stability. For example, electrostatic interactions between charged block
41 copolymers and oppositely charged active substances, polymer–metal complex
42 formation, and hydrogen bonding. In specific cases functional features may also be
43 added to the system, for example, by targeting molecule conjugation to the block
44 copolymer, or by the addition of another homopolymer to stabilize the micelle or active
45 substance, modify its release rate and/or increase the loading of the active substance.
46 In any given product, a proportion of the active substance could also be extra-block
47 copolymer micelle, free in bulk solution.

48 It should be emphasised that such block copolymer micelle products (as described
49 above) have a carefully designed structure in which the inner core typically serves as a
50 container for active substance and that is surrounded by an outer shell of hydrophilic
51 polymers. Additionally the chemistry of such block copolymer micelles may be designed
52 to ensure high stability after dilution on administration due to a low critical association
53 concentration (cac), to optimize the pharmacokinetics (PK) (targeting), and to control
54 the drug release, etc. Thus the dissociation of such block copolymer micelles may be
55 kinetically slow. These properties are different from traditional surfactant micelles used
56 to entrap/solubilise/aid the transport of drugs. Moreover, a block copolymer micelle
57 product can contain multiple components within the core including chemically bound
58 active substance, which in certain cases may be covalently bound.

59 Furthermore, it has been shown in non-clinical studies that block copolymer micelles
60 may have the potential to preferentially accumulate in solid tumors due to
61 microvascular hyperpermeability and impaired lymphatic drainage (known as the
62 enhanced permeability and retention (EPR) effect). The specific physicochemical
63 properties of block copolymer micelles, such as size, surface-charge, composition, and
64 stability can be important determinants of safety and efficacy in all proposed
65 applications.

66 Several block copolymer micelle products are currently in pre-clinical or in clinical
67 development, for example, products containing anti-tumor agents and proteins.

69 As block copolymer micelle products are of nano-scale size, contain more than one
70 component, and are purposely designed for specific clinical applications they may be
71 considered as nanomedicines.

72 This reflection paper discusses the general principles for assessing block copolymer
73 micelle products but does not aim to prescribe any particular quality, non-clinical or
74 clinical strategy.

75 Where applicable, it should be read in connection with the following ICH guidelines:

76 **ICH Guidelines**

- ICH Harmonised Tripartite Guideline Stability testing of new drug substances and products Q1A(R2)
- ICH Quality of biotechnological/biological products Q5A(R1)-Q5E (Q5E Note for Guidance on Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process)
- ICH Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A
- ICH Specifications: Test procedures and acceptance criteria for biotechnological/biological products Q6B
- ICH Pharmaceutical Development Q8(R2)
- ICH Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2)
- ICH Guidelines for Toxicokinetics and Pharmacokinetics S3A and S3B
- ICH Duration of Chronic Toxicity Testing in Animals (Rodent and Non rodent Toxicity Testing) S4
- ICH Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1)
- ICH Safety Pharmacology Studies for Human Pharmaceuticals S7A
- ICH The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals S7B
- ICH Immunotoxicology Studies for Human Pharmaceuticals S8
- ICH Nonclinical Evaluation for Anticancer Pharmaceuticals S9

2. Scope

This paper provides basic information for the pharmaceutical development, and non-clinical and early clinical studies of block-copolymer micelle drug products created to affect PK, stability and distribution of incorporated or conjugated active substances *in vivo*. Although the focus is on products designed for intravenous administration, the principles outlined in this reflection paper might also be considered to be applicable to block copolymer micelle products designed for other routes of administration. The active substance could be a low molecular weight chemical entity, nucleic acids, or a biological or biotechnologically derived entity (i.e. recombinant product), including, for example, peptides and proteins.

Due to the complexity of the system, i.e. whether or not the active substance is chemically bound, and/or additional stabilizers are used, it is recommended that an early dialogue with the regulators takes place to discuss the likely critical product attributes of each particular block copolymer micelle product. During this dialogue the sponsors are encouraged to discuss emerging methods that might be applied to define quality and non-clinical properties relevant to the proposed clinical application.

This document, being a reflection paper, should be read in connection with relevant ICH guidelines (listed above) and regional guidelines (Annexes I and II)¹.

¹ Post-marketing issues are not discussed. Drug products that use block copolymers as coating materials for nanoparticles of other materials such as homopolymers or metals are also not covered in this paper.

118

119 **3. Discussion**

120 **3.1 Chemistry, manufacturing and controls**

121 **3.1.1 Pharmaceutical Quality**

122 It is important to identify the critical quality attributes of block copolymer micelle
123 products that will have a major impact on the in vivo PK and pharmacodynamic (PD)
124 properties that may impact on safety and efficacy. Correctly identifying the parameters
125 that define relevant physicochemical properties of the block copolymer micelle product
126 is critical to ensure its quality.

127 **3.1.2 Description and composition**

128 The typical components of block copolymer micelle products are, the active substance,
129 the block copolymer, and in certain cases, other components such as stabilizing agents.

130 The critical quality attributes of block copolymer micelle product should be carefully
131 considered on a product specific basis. Of particular importance may be:

132 • the content of the block copolymer and active substance in the block
133 copolymer micelle product. These should be expressed both as the molar ratio
134 and the percentage of each by weight.

135 • the composition, mean molecular weight and polydispersity of the polymers
136 (homopolymers, copolymers etc.) used to synthesise the block copolymers (or
137 block copolymer-active substance conjugates)

138 • the composition, mean molecular weight and polydispersity of the block
139 copolymers used to create the block copolymer micelle.

140 Any acceptable ranges given should be fully justified.

141 **3.1.3 Quality characterisation**

142 The following are typical examples of properties, related to:

143 **A. Components containing block copolymers**

144 The chemical composition of block copolymers greatly impacts the driving force behind
145 polymer self-association, and therefore, size and physicochemical characteristics and *in*
146 *vitro* and *in vivo* stability of the resultant micelles. Crucial properties include:

- 147 • Chemical structure of the block copolymers:
- 148 • Chemical nature and stability of chemical linkage in the case of block copolymer-
149 active substance conjugate
- 150 • Impurity profile (e.g., macromolecular impurities)

151 **B. Block copolymer micelle products**

152 Properties relevant for the quality characterisation of the finished product are of
153 different types and include:

154 Properties related to the block copolymer micelle

- 155 • Block copolymer micelle size (mean and distribution profile)
- 156 • Morphology
- 157 • Zeta potential
- 158 • Association number

- 159 • Concentration dependency of the nano-structure (In some cases, this may be
- 160 expressed as critical micelle concentration (cmc), or critical association
- 161 concentration (cac). It should be noted that these parameters of some block
- 162 copolymers are too low to be measured using the current analytical techniques.)
- 163 • drug loading
- 164 • surface properties
- 165 • chemical structure
- 166 • physical state of the active substance
- 167 • in vitro stability of the block copolymer micelle in plasma and/or relevant media
- 168 • in vitro release of the active substance from the block copolymer micelle product
- 169 in plasma and/or relevant media
- 170 • in vitro degradation of the block copolymer in plasma and/or relevant media

171 Properties related to the manufacturing process

- 172 • validated process for reconstitution
- 173 • validated process for ensuring sterility

174 Properties related to the *in vivo* behaviour

- 175 • osmolarity
- 176 • fraction of active substance that is surface associated
- 177 • release rate and place of active substance release
- 178 • block copolymer degradation rate and place of degradation

179 Where the block copolymer component itself (not the active substance) has a biological
 180 activity which would have an impact on clinical efficacy and/or safety, its potency and
 181 physicochemical properties that are critical for its biological activity should be
 182 evaluated as part of characterisation.

183 A list of validated tests to be applied routinely to the block copolymer micelle product
 184 should be defined by the applicant and should be based on the parameters chosen to
 185 characterise the drug product including those described above, as appropriate.

186 Development of discriminating, in-vitro release methods is important for the purpose
 187 of:

- 188 • defining the release of the active substance or block copolymer-active substance
- 189 conjugate from the block copolymer micelle when in the circulation
- 190 • defining the release of the active substance or block copolymer-active substance
- 191 conjugate from the block copolymer micelle at the targeted site of action. The
- 192 proposed media should reflect the physiological environment of the block
- 193 copolymer micelle when in use.
- 194 • defining the stability on storage.

195 The methods used must be sensitive enough to ensure batch to batch consistency

196 This is particularly important to monitor in the case that a block copolymer-active
 197 substance conjugate is involved.

198 **3.1.4 Manufacturing process and process control**

199 A well-defined manufacturing process with its associated process controls is needed to

200 ensure that acceptable product is produced on a consistent basis. It is known that
201 small changes to block copolymer micelle products may significantly influence their
202 performance.

203 The manufacturing process should be controlled to ensure consistency in the product's
204 performance in terms of safety and efficacy. Data showing consistency in quality, and
205 controls for critical steps and intermediates should be provided. In addition to the
206 information recommended by the ICH Q8(R2) – pharmaceutical development,
207 recommendations specific to block copolymer micelle products are provided below.

208 ***Components containing block copolymers and/or block copolymer active***
209 ***substance conjugates***

210 Detailed descriptions of the synthetic process, extraction, and purification procedures
211 should be provided as applicable.

212 The source and specifications for any starting materials should be provided. In
213 particular, for polymeric starting materials, molecular weight and molecular weight
214 distribution should be clearly described. Impurities such as manufacturing impurities,
215 and macromolecular reaction by-products should be clearly specified.

216 Key intermediates in the manufacturing process should be identified and controlled.

217 Biotechnologically derived and/or entities of biological origin that are used as starting
218 materials or active substance should follow the requirement for medical use contained
219 in the ICH quality guidelines for biotechnological/biological products.

220 To identify the impact of a manufacturing process change, e.g. change in scale, a
221 careful evaluation of all foreseeable consequences for the product including process
222 validation/evaluation should be performed.

223 ***Block copolymer micelle products***

224 In the manufacturing process of block copolymer micelle products, micelle formation
225 process is critical. When micelle formation occurs spontaneously, the process of micelle
226 formation would be equal to the dispersion process of block copolymer. When other
227 methods are required for micelle formation, critical quality attributes associated with
228 the process (e.g. micelle size and solution transparency) should be controlled.

229 Since block copolymer micelle products contain highly-functional polymers, it is highly
230 recommended that appropriate quality control of intermediates (i.e. the block
231 copolymer) and/or the process, is undertaken based on the Quality by Design (QbD)
232 concept.

233 ***3.1.5 Product Specification***

234 Regarding definition of an acceptable specification for a block copolymer micelle
235 product (see guidelines ICH Q6A or Q6B), it is recommended that the applicant
236 engages in an *early dialogue with the regulators*. Additional testing specific to block
237 copolymer micelle products may be needed.

238 ***Components containing block copolymers***

239 A detailed description of the tests, procedures, and acceptance criteria for block
240 copolymers and/or block copolymer-active conjugates should be provided. Evaluation
241 of the polymer, such as mean molecular weight and its distribution should be obtained.
242 The composition of each component should also be obtained.

243 ***Block copolymers micelle products***

244 Because drug products based on block copolymers are functional polymeric structures,
245 the critical quality attributes should be defined in respect of the functions for the
246 intended use. These attributes will include particle size, release rate of the active
247 substance from the micelle, and potency if the active substance is a
248 biotechnological/biological entity. Where present, the composition regarding average
249 number of targeting-molecules conjugated to the polymeric micelle to promote active
250 targeting should be justified.

- 251 • it should be noted that block copolymer micelle products may be a mixture of
252 block copolymer micelles and block copolymer unimers (with or without bound
253 active substance), depending on the individual characteristics of the block
254 copolymers, the active substance and the test conditions used. Therefore,
255 analytical tests should be performed considering the product's form under
256 appropriate test conditions and procedures. The test concentration should be
257 carefully considered, because dilution of block copolymer micelle products may
258 cause disassociation of micelles and result in an increased proportion of unimers.
- 259 • considerations relating to identity and purity should take into account both the
260 active substance and the block copolymers. Impurities, including possible
261 synthetic macromolecular by-products, should be evaluated. Undesirable
262 aggregates, precipitates, and degradation products will be also considered as
263 impurities.
- 264 • potency, if the active substance is a biotechnological/biological entity.

265 Other attributes are as follows:

- 266 • Physicochemical properties of block copolymer micelle products determined to be
267 critical to product quality. However, not all the characterization tests need to be
268 included in the specifications. (See section 3.1.3 on Physicochemical
269 characteristics of block copolymer micelles).
- 270 • Assay of incorporated (or conjugated) and unincorporated (or unconjugated)
271 active substance.
- 272 • Assay of block copolymers or weight fraction to active substance

273 Stability should be considered in the context of the proposed clinical use and justified
274 in the specification.

275 **3.1.6 Stability**

276 The concepts in ICH Q1A(R2) apply to the design of stability studies for block
277 copolymer micelle products. Those in ICH Q5C also apply to biotechnological/biological
278 entities.

279 In general, stability studies should address the physical and chemical stability of the
280 active substance, the block copolymers (and if present block copolymer-active
281 substance conjugates), and the resultant micelles. Typical attributes that may be
282 evaluated include, but are not limited to:

283 Physical stability

- 284 • mean block copolymer micelle size
- 285 • release of the incorporated or conjugated active substance
- 286 • secondary aggregation
- 287 • in vitro release of active substance, as appropriate under appropriate test
288 conditions

289 Chemical stability

- 290 • stability of active substance
- 291 • stability of block copolymer components (e.g. degradation of polymers)
- 292 • if present, stability of block copolymer-active substance conjugates

293 In vitro methods, using conditions relevant to the proposed use, should be used to
294 determine

- 295 • the release rate of the active substance entrapped in the block copolymer micelles
- 296 • the rate of release of active substance chemically bound to block copolymer
297 micelles

298 **3.1.7 Changes in manufacturing during development**

299 If there are changes in manufacturing critical process parameters or equipment used
300 for manufacture, complete characterization of the block copolymer micelle product may
301 be warranted on a case-by-case basis. Approaches to determining the impact of any
302 process change will vary with respect to the specific manufacturing process, the
303 product, the extent of the manufacturer's knowledge and experience with the process
304 and development data provided.

305 It is important to also consider applying the principles for assessing the comparability
306 studies of products before and after changes made in the manufacturing process, as
307 those developed for Biological Medicinal Products. The principles of comparability
308 studies are outlined in section 1.4 of ICH Q5E (Note for Guidance on
309 Biotechnological/Biological Products Subject to Changes in their Manufacturing Process).

310

311 **3.2 Non-clinical studies**

312 **3.2.1 General Considerations**

313 Significant changes in pharmacokinetic characteristics can occur when an active
314 substance is administered as a block copolymer micelle product, i.e. volume of
315 distribution and clearance may be changed, half-life prolonged and tissue distribution
316 changed. Significant changes not only in the PK characteristics but also in the PD and
317 safety of the active substance can also occur when it is administered as a block
318 copolymer micelle product. Moreover, it has been noted that certain block copolymers
319 (not containing an active substance) can display inherent biological activity, which
320 would have an impact on clinical efficacy and/or safety. Cellular uptake of block
321 copolymer micelle entrapped active substance may be limited to the endocytic route.

322 The PK characteristics of the block copolymer micelle product could be dependent on:

- 323 • the rate of clearance of the block copolymer micelle containing entrapped or
324 chemically bound active substance
- 325 • the rate of dissociation of the block copolymer micelle. This may lead to release of
326 block copolymer unimers (with or without bound active substance) that would
327 have lower molecular weight (smaller size characteristics) and may display
328 different clearance characteristics
- 329 • the rate of release of entrapped active substance from the block copolymer
330 micelle
- 331 • the rate of release of active substance chemically bound to the block copolymer
332 unimer

- 333 • the rate of degradation of the block copolymer
- 334 • clearance and metabolism of free active substance.
- 335 • the distribution of the block copolymer micelle
- 336 • interaction of the block copolymer micelle with plasma or serum proteins or blood
- 337 cells

338 The rate and location of in vivo active substance release is a crucial parameter which
339 often determines the toxicity and efficacy. An attempt should be made to develop the
340 necessary methodology to define active substance release.

341 All non-clinical studies should be conducted using well-characterised block copolymer
342 micelle product and the rate of micelle dissociation and product stability should be
343 known under the chosen test conditions.

344 **3.2.2 Non-clinical Pharmacokinetics**

345 **Analytical Methods**

346 Validated analytical techniques should be developed, that are capable of measuring the
347 concentrations of active substance both in total and in free form in blood, plasma or
348 serum, and the total concentration of active substance in organs and/or tissues.

349 **Pharmacokinetics**

350 As the PK behaviour of block copolymer micelle products can be very different from
351 that of the active substance administered without the block copolymer micelle carrier
352 and this can impact significantly on efficacy and safety, in vivo PK should be
353 determined. The choice of appropriate species and models to investigate in vivo PK,
354 and release of the active substance should be justified in respect of proposed clinical
355 use and the composition of the block copolymer micelle.

356 As physicochemical parameters such as size, surface-charge and morphology may
357 impact on the distribution of block copolymer micelle product, the effect of variability in
358 such parameters on distribution should be shown to justify the product specification.
359 Therefore, in addition to the information recommended in the ICH S3 (S3A and S3B),
360 S6(R1) and M3 (R2), the following parameters specific to block copolymer micelle
361 products should be assessed:

- 362 • PK parameters such as C_{max}, half-life, and AUC, of the block copolymer micelle
- 363 product both for total active substance and for free active substance in blood,
- 364 plasma, or serum.

365 PK parameters should be measured at different dose levels and at appropriate
366 time points.

- 367 • Distribution of the block copolymer micelle products in organs and/or tissues
- 368 relevant to proposed clinical use and route of administration. Specifically total
- 369 amounts of active substance may be required - see analytical methods. A
- 370 distribution time profile should be obtained using multiple time points with
- 371 justification of the time course of the study.

- 372 • Sampling time points and sampling duration should be carefully selected so as to
- 373 accurately quantify the time course of the concentrations of active substance
- 374 both in total and in free form and metabolites in blood, plasma or serum, and
- 375 the total concentration of active substance and metabolites in organs and/or
- 376 tissues. Some factors should be considered for the sampling schedules, for
- 377 example, the block copolymer micelle stability after administration, and the
- 378 profile of localization to specific organs and/or tissues. In particular, samples

taken in the initial distribution phase (e.g. <15 min) are considered very informative for calculating the distribution volume to estimate the stability of block copolymer micelles in blood circulation.

- Measurement of active substance metabolites in blood, plasma or serum and maybe organs and/or tissues is especially important when the metabolite is acknowledged to be the primary active compound. If one or more metabolites have substantial clinical activity then it might be necessary to compare their kinetics, and where necessary, toxicokinetics, to determine accumulation following multiple doses.
- Comparing the PK of the block copolymer micelle product and the active substance administered by itself is recommended. Such comparative studies are also considered useful to demonstrate a claimed pharmacokinetic advantage of the block copolymer product against the active substance administered by itself.
- It may also be important to consider the protein and cellular interaction of block copolymer micelles administered intravenously as these factors are known to have potential to influence the distribution, stability and safety of nanomedicines.

The metabolic and excretion pathways of the active substance should be determined and fully characterized after administration of the block copolymer micelle product. Furthermore, the metabolic and excretion pathways of the micelle constituents are by themselves of interest. Their detailed characterization is needed unless otherwise justified.

If there is concern that components of the block copolymer micelle drug products may cause drug-drug interactions, for example by modulating membrane transporters such as p-glycoprotein, an appropriate evaluation should be carefully undertaken.

3.2.3 Non-clinical pharmacodynamics

The non-clinical pharmacodynamic studies should include demonstration of pharmacodynamic response in appropriately justified in vitro (where possible) and in vivo models. In vivo evaluation should involve an appropriate route of administration, justified dose levels and a justified dosing regimen depending on proposed clinical application. Appropriateness of the pharmacological model should be discussed in respect of the PK of the block copolymer micelle product, and of the PD and PK of the active substance when administered by itself.

The chemical composition and physicochemical properties of a block copolymer micelle product affect properties including size, surface-charge, and the rate of release of the active substance. Some important factors to consider when designing studies to discuss the mechanisms of action include:

- the fate of active substance (the location and rate of in vivo active substance release)
- the fate of the micelles (block copolymers or other stabilizing components) following administration and/or cellular entry by endocytosis or other mechanisms.

The PD effect of the micelles should be assessed using in vitro and in-vivo pharmacodynamic models.

3.2.4 Safety Pharmacology

When applicable (e.g. for block copolymer micelle drugs out of the scope of ICH S9) the core battery of safety pharmacology studies should be conducted, in accordance with ICH M3 (R2), ICH S7A and ICH S7B.

3.2.5 Toxicology

For the non-clinical evaluation of toxicities of block copolymer micelle products, the recommendations in the ICH safety guidelines especially of S4, S6(R1) and S9 and M3 (R2) should be followed.

Relevant toxicity studies of the block copolymer micelle product should be conducted to assess both the toxicological profile and exposure-response relations according to the ICH safety guidelines.

Toxicokinetics

In addition to blood, plasma, or serum concentration, the active substance should be measured in the target tissue(s) and toxicologically relevant organs related to proposed clinical use.

Additional studies

Depending on the physicochemical and/or pharmacokinetic characteristics of the block copolymer micelle product and/or the block copolymer used for its manufacture, target organ function evaluation may be necessary.

Certain nanomedicines have the potential to induce infusion reactions. Studies designed to investigate complement activation, hematotoxicity, antigenicity, and/or immunotoxicity (ICH S8) should be considered depending on the characteristics of the block copolymer micelle product.

3.3 Considerations for first-in-human studies

Block copolymer micelle products are often designed to change the distribution of active substance. Therefore, in addition to the information recommended in the ICH S3 (S3A and S3B), S6(R1), M3 (R2) and PMFS/ELD Notification NO. 0402-1, April 2, 2012 or EMEA/CHMP/SWP/28367/2007 (as appropriate), when considering first-in-human studies it will be essential to consider non-clinical pharmacokinetic data specific to the block copolymer micelle product e.g. the block copolymer micelle, the active substance, the proposed clinical use and the route of administration, using sampling time points and sampling duration that is carefully selected so as to accurately quantify the time course of block copolymer micelle products for total active substance and for free active substance and metabolites, as follows:

- PK parameters such as C_{max}, half-life, and AUC, of block copolymer micelle products both for total active substance and for free active substance in blood, plasma or serum.
- A sufficient number of samples to adequately describe the plasma concentration-time profile should be collected. Frequent sampling at early time points are considered useful for providing reliable information about the initial distribution process. Generally the sampling schedule should also cover the plasma concentration time curve long enough to provide a reliable estimate of the total extent of exposure.
- Distribution of the block copolymer micelle products in target lesion and major organs; specifically total amounts of active substance in target lesion and major organs and their time profiles at multiple time points over an adequate period of time.

The starting dose for first-in-human studies should be chosen in compliance with ICH M3(R2), and regional guidelines, and following careful consideration of all related non-clinical data, including critical product attributes, pharmacological dose-response, PK,

473 and pharmacological/toxicological profile as discussed in sections 3.1 and 3.2 above.
474 Dose-limiting toxicity in humans can be determined in a similar way to that of
475 conventional drugs, except for hypersensitivity reactions because these reactions are
476 not always dose-dependent.

477 Potential critical quality attributes for each block copolymer micelle product should be
478 identified and used to evaluate consistency as discussed in section 3.1. Consistency of
479 the quality attributes should be confirmed between the products used for non-clinical
480 studies and those for first-in-human studies, and test procedures should be established
481 before commencement of first-in-human studies. If the manufacturing process used to
482 prepare block copolymer micelle product for non-clinical studies is changed before first-
483 in-human studies comparability should be demonstrated or otherwise justified.

484 Stability data that ensure the block copolymer micelle stability throughout the first-in-
485 human studies are required.

486

487 **4. Conclusions**

488 Given the complexity of block copolymer-micelle products and the fact that experience
489 with such products is limited companies are advised to seek product-specific scientific
490 advice regarding specific questions on the data requirements.

491

492 **Glossary**

493 The purpose of this glossary is to describe terms as they are used in this RP.

494 1) Active substance: Molecule which shows the main therapeutic effect

495 2) Block copolymer: More than two kinds of polymer connected in series to form such
496 as AB or ABA type copolymer (or others).

497 The block copolymer is also called a unimer: the minimum unit from which the block
498 copolymer micelle is prepared. The active substance may be chemically bound to the
499 unimer.

500 3) Block copolymer micelle: A micelle which consists of block copolymers. Active
501 substances can be incorporated into the inner core of the block copolymer micelle by
502 chemical conjugation (including covalent conjugation) or by physical entrapment.

503 4) Block copolymer micelle product: "Medicinal product", a drug product which contains
504 active substance, block copolymers and in certain cases, other ingredients.

505 5) Free active substance: Active substance present in the drug product that is not
506 incorporated within the block copolymer micelle by chemical conjugation or by physical
507 entrapment.

508

509 Free active substance may be released from the block copolymer micelle product after
510 administration. In this reflection paper, the term "free" does not suggest the
511 disassociation of active substances from plasma or serum proteins.

512

513 6) Biological activity: The specific ability or capacity of a product to achieve a defined
514 biological effect.

515 7) Potency (expressed in units): In the case that the active substance is a protein, the
516 quantitative measure of biological activity based on the attribute of the product which
517 is linked to the relevant biological properties, whereas, quantity (expressed in mass) is
518 a physicochemical measure of protein content.

Regional guidelines

Annex I

MHLW

- ICH Harmonised Tripartite Guideline Stability testing of new drug substances and products Q1A(R2)[June 3, 2003, PMSB/ELD Notification No.0603001]
- ICH Quality of biotechnological/biological products Q5A(R1)-Q5E (Q5E Note for Guidance on Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process) [February 22, 2000, PMSB/ELD Notification No.329 (Q5A(R1)), January 6, 1998, PMSB/ELD Notification No.3 (Q5B), January 6, 1998, PMSB/ELD Notification No.6 (Q5C), July 14, 2000, PMSB/ELD Notification No.873 (Q5D) and April 26, 2005, PFSB/ELD Notification No.0426001 (Q5E)]
- ICH Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A [May 1, 2001, PMSB/ELD Notification No.568]
- ICH Specifications: Test procedures and acceptance criteria for biotechnological/biological products Q6B [May 1, 2001, PMSB/ELD Notification No.571]
- ICH Pharmaceutical Development Q8(R2) [June 28, 2010, PFSB/ELD Notification No.0628-1]
- ICH Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2) [February 19, 2010, PFSB/ELD Notification No.0219-4]
- ICH Guidelines for Toxicokinetics and Pharmacokinetics S3A and S3B [July 2, 1996, PMSB/ELD Notification No.443 and PMSB/ELD Notification No.442]
- ICH Duration of Chronic Toxicity Testing in Animals (Rodent and Non rodent Toxicity Testing) S4 [April 5, 1999, PMSB/ELD Notification No.655]
- ICH Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1) [March 23, 2012, PFSB/ELD Notification No.0323-1]
- ICH Safety Pharmacology Studies for Human Pharmaceuticals S7A [June 21, 2001, PMSB/ELD Notification No.902]
- ICH The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals S7B [October 23, 2009, PFSB/ELD Notification No.1023-4]
- ICH Immunotoxicology Studies for Human Pharmaceuticals S8 [April 18, 2006, PFSB/ELD Notification No.0418001]
- ICH Nonclinical Evaluation for Anticancer Pharmaceuticals S9 [June 4, 2010, PFSB/ELD Notification No.0604-1]
- Guidelines for Non-clinical Pharmacokinetic Studies [June 26, 1998, PMSB/ELD Notification No. 496]
- Guidance for Establishing Safety in First-in-Human Studies during Drug Development [April 2, 2012, PFSB/ELD Notification No. 0402-1]

Annex II
EMA

- ICH Harmonised Tripartite Guideline Stability testing of new drug substances and products Q1A(R2) [CPMP/ICH/2736/99]
- ICH Quality of biotechnological/biological products Q5A-Q5E (Q5E Note for Guidance on Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process) [CPMP/ICH/295/95 (Q5A(R1)), CPMP/ICH/139/95 (Q5B), CPMP/ICH/138/95 (Q5C), CPMP/ICH/294/95 (Q5D) and CPMP/ICH/5721/03 (Q5E)]
- ICH Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A [CPMP/ICH/367/96]
- ICH Specifications: Test procedures and acceptance criteria for biotechnological/biological products Q6B [CPMP/ICH/365/96]
- ICH Pharmaceutical Development Q8(R2) [EMA/CHMP/167068/2004]
- ICH Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2) [CPMP/ICH/286/95]
- ICH Guidelines for Toxicokinetics and Pharmacokinetics S3A and S3B [CPMP/ICH/384/95 and CPMP/ICH/385/95]
- ICH Duration of Chronic Toxicity Testing in Animals (Rodent and Non rodent Toxicity Testing) S4 [CPMP/ICH/300/95]
- ICH Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1) [EMA/CHMP/ICH/731268/1998]
- ICH Safety Pharmacology Studies for Human Pharmaceuticals S7A [CPMP/ICH/539/00]
- ICH The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals S7B [CPMP/ICH/423/02]
- ICH Immunotoxicology Studies for Human Pharmaceuticals S8 [CHMP/167235/2004]
- ICH Nonclinical Evaluation for Anticancer Pharmaceuticals S9 [EMA/CHMP/ICH/646107/2008]
- Guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products [EMA/CHMP/SWP/28367/2007]
- Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (non-polymeric surfactants) EMA/CHMP/QWP/799402/2011
- Draft Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product EMA/CHMP/806058/2009
- Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products EMA/CHMP/SWP/28367/07

- 610 • Guideline on the Investigation of Pharmacokinetic Drug Interactions
611 (CPMP/EWP/560/95/Rev. 1)
- 612 • Guidance for Industry. Bioanalytical Method Validation U.S. Department of Health
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