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4 Reflection paper on the data requirements for intravenous

- ⁵ liposomal products developed with reference to an
- 6 innovator liposomal product
- 7 Draft

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¹ The QWP has been involved in the discussions and agreed to the draft.

¹⁰ Reflection paper on the data requirements for intravenous

- ¹¹ liposomal products developed with reference to an
- 12 innovator product

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17 **1. Introduction**

18 There has been a significant interest to develop drug delivery methods for potent albeit sometimes 19 toxic, highly lipophilic/poorly water soluble, unstable compounds, or for tissue targeting of highly water 20 soluble compounds. One of the strategies has been encapsulation of the active substance(s) in the 21 aqueous phase of a liposome, or incorporation or binding to the lipid components. Liposomes are 22 classically described as vesicles composed of one or more concentric lipidic bi-layers. Such variants 23 include, but are not limited to, multi-vesicular liposomes, polymer-coated vesicles and lipidic 24 complexes. In any given product, a proportion of the active substance could also be extra-liposomal, 25 free in bulk solution.

Early parenteral liposomal products were found to have a number of critical pharmacokinetic properties including rapid recognition and removal by the monocyte phagocyte system (MPS) and premature drug-release (instability). It was also recognized that the physicochemical properties of the liposomes, such as particle size, membrane fluidity, surface-charge and composition were relevant determinants of such in vivo behaviour. Some formulations were found to benefit from the addition of sterols (e.g. cholesterol), size reduction and surface modification with covalently linked polymers (e.g. polyethylene glycol [PEG]), to provide significant improvements.

33 Contrary to products where the active substance is in simple solution, liposomal medicinal products 34 have formulation-specific distribution characteristics in-vivo and similar plasma concentrations may not correlate to equivalent therapeutic performance. The complete characterisation of the 35 36 pharmacokinetics and tissue distribution of a new liposomal product is critical to establish safe and 37 effective use because formulation differences may substantially modify efficacy/safety due to specific cell interactions and distribution characteristics which are not detectable by conventional 38 39 bioequivalence testing alone. The aims of developing the originator and the evidence supporting its use 40 should be taken into account when designing the non-clinical and clinical programme for the liposomal 41 products developed with reference to that particular originator.

The reference liposomal product used for comparability investigations should be sourced from withinthe EU and should be used as a comparator in all proposed characterization studies.

This document discusses the principles for assessing liposomal products developed with reference to an innovator liposomal product but does not aim to prescribe any particular analytical, nonclinical or clinical strategy.

- 47 This reflection paper should be read in connection with the following documents:
- 48 Directive 2001/83/EC, as amended
- Part II of the Annex I of Directive 2001/83/EC, as amended
- CHMP/437/04 Guideline on similar biological medicinal products
- Annex II to Note for Guidance on Process Validation CHMP/QWP/848/99 and
 EMEA/CVMP/598/99 Non Standard Processes (CPMP/QWP/2054/03)
- Guideline on similar medicinal products containing biotechnology-derived proteins as active
 substances: quality issues
- ICH topic Q5E Comparability of biotechnological/biological products
- ICH topic S6 Note for guidance on Pre-clinical Safety Evaluation of Biotechnology-Derived
 Pharmaceuticals (CPMP/ICH/302/95)

- ICH topic E9 statistical principles for clinical trials Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)
- ICH topic E10 Note for guidance on choice of control group in clinical trials (Guideline on the choice of the non-inferiority margin (CPMP/EWP/2158/99)
- Points to consider on switching between superiority and non-inferiority (CPMP/EWP/482/99)
- Note for guidance of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98, rev 1 corr *)

65 **Scope**

This reflection paper is intended to assist in the generation of relevant quality, non-clinical and clinical data to support a marketing authorisation of intravenous liposomal products developed with reference to an innovator liposomal product. Hence, this document should facilitate a decision on the following issues:

- pharmaceutical data needed as evidence of product comparability between test and
 reference or after changes to a liposomal product, to support comparative safety and
 efficacy
- Necessity of pre-clinical and clinical studies (including 'usual' bioequivalence studies) and
 circumstances which may allow to waive certain studies

The principles outlined in this reflection paper might also be considered to be applicable to other novel types of "liposome-like" and vesicular products which may be under development including those to be administered by routes other than intravenous administration.

78 **2. Discussion**

79 2.1 Pharmaceutical Quality

80 The critical quality attributes of liposomal formulations have a major impact on the in vivo 81 pharmacokinetic (PK) and pharmacodynamic (PD) properties, since:

- the active substance release rates from liposomes can affect PK and PD and therefore the
 safety and efficacy profile of the medicinal product
- usually the entrapped active substance is biologically not available and protected from
 metabolism as long as it is entrapped in the liposome
- the PK of the encapsulated substance may be controlled by the PK of the carrier (i.e. the
 liposomal formulation) which is influenced/determined by the physicochemical properties of the
 liposomes and by the physical state of the encapsulated drug substance

89 Due to the complexity of liposomal formulations, establishing pharmaceutical comparability cannot 90 substitute entirely for non-clinical and/or clinical data but may justify reduction in the amount of non-91 clinical and clinical studies.

92 **Quality Characterisation**

93 Correctly identifying the parameters that define relevant physicochemical properties of a liposomal 94 product is critical to ensure its quality. The following general parameters should be addressed in the 95 submission of all types of liposomal products:

96 • critical discussion of the lipidic components (description, source and characterisation,

- 97 manufacture, specification and stability);
- quality, purity and stability of other nonlipidic starting materials and critical excipients;
- identification and control of key intermediates in the manufacturing process;
- active substance/lipidic moiety ratio at relevant manufacturing steps to ensure consistent
 formulation;
- liposome morphology, size and size distribution,
- fraction of encapsulated active substance (amount of free/entrapped)
- assay of lipidic components;
- 105 osmolarity;
- stability of the active substance, lipids and functional excipients in the finished product,
 including quantification of critical degradation products (e.g. Lyso phosphatidylcholine,
 oxidated/hydrolytic moieties)
- stability studies under proposed in-use conditions;
- *in vitro* drug substance release rate from the liposome in relevant media and stress conditions;
- validated process for reconstitution and/or pharmacy preparation.

Depending on the specific function of the liposomal formulation (e.g. modification of the distribution of active substance by encapsulation for improved safety profile or modification of liposomal pharmacokinetics by pegylation), the additional parameters below should be also considered in the submission:

- maintenance of liposomal formulation integrity in plasma;
- characterisation/specification testing for lipid bilayer phase transition; temperature and/or
 liposomal `surface' charge;
- confirmation of physical state of the active substance inside the liposome (e.g. precipitation in the case of doxorubicin),
- fraction of drug that is surface bound;
- for pegylated liposomal formulations:
- 123 details of linkage chemistry (PEG-lipid),
- 124 molecular weight of pegylated lipid and size distribution,
- 125 disposition of PEG at surface,
- stability of pegylation;
- 127 A list of tests to be applied routinely to the liposomal product should be defined and should be based 128 on the parameters used to characterise the formulation as described above.
- 129 Discriminating validated in-vitro release methods should be developed to:
- monitor the simulated release of the active substance from the liposomes when in circulation and if possible around the targeted site of action (e.g. different pH environments at site of action). The proposed media should reflect the physiological environment of the liposomes when in use.

• monitor stability on storage, and be sensitive to ensure batch to batch consistency.

135 Establishing pharmaceutical comparability

136 The qualitative and quantitative composition of the developed product should be identical or closely 137 match the reference product.

It is acknowledged that normally the applicant of a liposomal formulation developed with reference to 138 139 an innovator product will have no access to information about the manufacturing process of this 140 reference. Therefore, extensive state of the art characterisation studies should be applied to both 141 products in parallel in order to demonstrate with a high level of assurance that the quality is comparable. The comparability studies should include the tests mentioned in the Quality 142 143 Characterisation section suitable to adequately characterise the quality of the test and reference 144 liposomal products and particularly relate to their performance in vivo. Differences to the reference product identified in the comparability investigations should be addressed and thoroughly evaluated. 145

- 146 In addition to the characterisation studies conducted under normal conditions, comparative stress test 147 studies of both products, i.e. the liposomal product developed and the innovator, could be an option to 148 investigate the outcome on degradation and other physicochemical performance characteristics of the 149 liposomal formulation.
- 150 All batches of the reference product used in the characterization studies should be analyzed within 151 their shelf-life period and should be stored by the recommended storage conditions prior to analysis.

152 Pharmaceutical Development of the Applicant's Product

A well-defined manufacturing process with its associated process controls assures that acceptable product is produced on a consistent basis. It is known that small changes to liposomal products can significantly influence their performance. Approaches to determining the impact of any process change will vary with respect to the specific manufacturing process, the product, the extent of the manufacturer's knowledge and experience with the process and development data provided. Comparative investigations (see *Quality Characterisation section*) should be considered when a change is introduced into the manufacturing process during development.

160 In vivo studies may be necessary to demonstrate that the changes do not impact the safety and 161 efficacy profile of the product when results from physicochemical testing indicate a change in the 162 properties of the product.

163 It is recommended to consider basic principles as outlined in section 1.4 of ICH Q5E (Note for Guidance 164 on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process).

165 2.2 Non-Clinical and Clinical Requirements

166 General Aspects

167 The documentation required to support regulatory approval of a liposomal formulation developed with 168 reference to an innovator product should be extensive and detailed enough to warrant the conclusion 169 of equivalent efficacy and safety as compared to the innovator product. In general, required non-170 clinical studies to be performed prior to bioequivalence testing should include comparative 171 investigation of pharmacokinetics, tissue distribution, toxicology and pharmacological studies. However, 172 the complexity of the particular liposomal formulation will determine whether comparative non-clinical 173 studies can be reduced. Therefore, it may be decided on a case-by-case basis which studies could be 174 waived.

175 In the comprehensive evaluation of the new liposomal product the body of evidence obtained in 176 quality, non-clinical and clinical studies must be considered as a whole. If e.g. any relevant difference 177 is found in non-clinical studies for the liposomal formulation developed with reference to the innovator 178 then critical re-assessment of physico-chemical product characteristics is advised in order to clarify 179 possible reasons of detected deviations rather than proceeding to the next clinical investigation. 180 Controversy between the data generated to support product similarity would contradict the similarity 181 approach referencing the innovator and can be a source of serious regulatory concern.

182 2.2.1 Non-Clinical Studies

183 Non-clinical pharmacokinetic studies

184 Some pharmacokinetic aspects of liposomal products with regard to their performance in humans can 185 be depicted in animal and cellular models. However, the choice of appropriate species and models to 186 investigate the in-vivo release of the drug from liposomes should be justified with special emphasis on 187 areas such as accumulation in target organs, pharmacokinetics and distribution. Single and multiple 188 dose studies at different dose levels may be needed to support the claim of similar pharmacokinetics. 189 In addition to the systemic exposure, similarities in the distribution and elimination should be 190 demonstrated. The active substance concentration in tissues relevant to the toxicity and/or efficacy of 191 the product should be determined and quantitatively compared with the reference liposomal product.

192 Non-clinical pharmacodynamic studies

- 193 The non-clinical pharmacodynamic studies should include
- demonstration of similarity in pharmacodynamic response at different dose levels using
 adequate models
- in-vitro tests which characterize the interaction between liposomes and target cells or with
 other cells where the interaction is toxicologically relevant and important.

198 Toxicological studies

199 In general toxicity studies may not be needed, however depending on the outcome of pharmaceutical 200 comparability investigations, and nature of the toxicity of the product, the company may need to 201 conduct appropriate toxicity studies.

202 2.2.2 Clinical Studies

203 Comparative pharmacokinetic studies

204 General considerations

205 Significant changes in pharmacokinetic characteristics are evident when an active substance is 206 administered in a liposomal formulation, i.e. volume of distribution and clearance are reduced and half-207 life prolonged. The clearance of the liposomal active substance is dependent on:

- 208 (1) the rate of clearance of the liposomal carrier itself,
- 209 (2) the rate of release of entrapped drug from the liposomal carrier, and
- 210 (3) the rate of clearance and metabolism of free drug upon its release.
- The rate and location of in vivo drug release is a crucial parameter usually determining toxicity and efficacy.

Therefore, the pharmacokinetics of the developed similar liposomal product should always be compared with the innovator's product. Only certain aspects of the conventional bioequivalence approach are applicable and in some cases additional requirements should be set on a case-by-case basis. 217 Comparative human pharmacokinetic investigations should demonstrate not only the similarity of 218 exposure of the non-encapsulated and liposome encapsulated drug but they should also demonstrate 219 similar distribution and elimination characteristics. Validated methods to determine encapsulated and 220 free concentration of the active substance in biological samples (e.g. whole blood, plasma) should be 221 employed in pharmacokinetic studies.

222 Dose to be investigated

Pharmacokinetic behaviour might be dose-dependent and hence, the pharmacokinetics of the new formulation and the reference should be compared in the whole dose range unless linearity has been demonstrated in the recommended dose range or the most sensitive dose can be determined and justified. If the product is administered at several doses for different therapeutic indications, a pharmacokinetic study with each particularly recommended dose is needed unless linearity has been demonstrated.

229 Design considerations

If the product could not be administered to healthy volunteers, a pharmacokinetic study can be performed in patients. If a single-dose study is not feasible (i.e. active substance is not tolerable in healthy volunteers) multiple dose pharmacokinetic studies in patients are acceptable.

233 Analytes to be measured

The validated bioanalytical method should reliably quantify encapsulated and non-encapsulated drug substance. Quantification of at least one metabolite regardless of its pharmacological activity may facilitate to assess and compare a release rate, since metabolism of the active substance takes place only after release from the liposomes. If there are several metabolites then the choice of metabolite should be justified on kinetic grounds. If one or more metabolites have significant clinical activity then it might be required to compare their kinetics as well.

240 Pharmacokinetic parameters to be measured and reported

Ideally, the evaluated pharmacokinetic characteristics should allow comparison of the rate at which the active substance is released from the liposomes, since this will determine the onset and duration of the therapeutic effect. However, conventional pharmacokinetic metrics such as AUC and Cmax might not give sufficient indication of the rate of release at the target sites. Therefore, distribution and elimination should be investigated in addition to rate and extent of release. When relevant, rate and extent of excretion of active substance in urine should be compared.

For liposomes with release over a longer period of time, clearance, volume of distribution, terminal half-life and partial AUCs (e.g. 0-24h, 24-48h etc) should be evaluated descriptively. This enables further characterisation of the integrity of liposomes and their uptake by peripheral tissues/reticuloendothelial system. Additionally, further descriptive parameters could be considered e.g. inter-compartmental clearance and volume of the peripheral and central compartments.

It is recommended to determine the ratio of non-encapsulated to encapsulated drug concentration overtime.

254 Acceptance criteria

255 Similarity should be demonstrated for the encapsulated and non-encapsulated drug. Generally, the 256 90% confidence intervals of Cmax, AUCinf and AUCt ratios should be within 80 - 125%. Additional 257 metrics might include partial AUCs, or acceptance criteria for the metabolite.

258 Assessment of efficacy

In general, the necessity for a clinical efficacy trial(s) besides the obligatory clinical pharmacokinetic studies is decided on a case-by-case basis depending on the sensitivity of the non-clinical models and clinical PK data to detect differences between innovator and the liposomal product developed with reference to it, and the complexity of the formulation.

Carrying out additional therapeutic equivalence studies are always required if the formulations differ in terms of qualitative composition. As an example clinical studies including therapeutic equivalence studies might be required in cases when polymers are attached to lipids by means of different linking methods. When developing a liposomal product with reference to an innovator product all attempts should be made to demonstrate equivalence of pharmaceutical quality of formulations and similarity in non-clinical and clinical pharmacokinetic studies.

269 Safety issues

Acute infusion reactions are relatively common with liposomal formulations. However, the frequency of such side effects is expected to be comparable unless the investigative products differ with respect to qualitative composition (e.g. different excipients). Use of animal models and unloaded (empty) liposomes for the investigation of hypersensitivity reactions may be necessary.

274 **3.** Conclusion

The experience with liposomal formulations developed with reference to an innovator is limited. As only rather general recommendations can be given in this reflection paper companies are advised to seek product-specific scientific advice regarding specific questions on the data requirements for

278 demonstration of comparability of liposomal formulations.