05 March 2012
EMA/CHMP/QWP/686808/2011
Compliance and Inspection

Overview of comments received on ' Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (non-polymeric surfactants) ' (EMA/CHMP/QWP/574767/2010)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
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2	Novartis
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1. General comments – overview

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1	Surfactant solubilizers are a possible solution to the formulation of poorly water-soluble drugs for parenteral use. In recent years the water solubility of drug candidates has declined and an increasing number of investigational drugs fall into biopharmaceutics classes 2 and 4; thus we expect these formulation types to continue to be studied for the foreseeable future.	The company's comments are acknowledged. Revision of the RP is not required.
1	Although formulation challenges arise from any therapeutic area, the Complex Parenterals team is most frequently called on to solve such formulation problems for oncology and infection therapeutics. Thus the dosing is normally acute and relatively high doses are the norm. The primary reason that we have not progressed surfactant-solubilized products to date is that they are unable to solubilize the required doses of drug using toxicologically acceptable levels of surfactant.	The company's comments are acknowledged. Revision of the RP is not required.
1	AstraZeneca welcomes guidelines for the use of surfactant solubilizers, due to the complexity of these formulations and the potential for physicochemical problems to arise in their use. Broadly, we are in agreement with the proposals, but our expertise has led to a number of additional points which may be of value.	The company's comments are acknowledged. Revision of the RP is not required.
2	The availability of a reflection paper on the subject of solubilising micellar systems for intravenous administration is highly appreciated.	The company's comments are acknowledged. Revision of the RP is not required.
2	We would recommend focusing on the major risk factors for surfactant use in this route: 1. Physical stability solutions during use 2. Compatibility with injection/infusion devices 3. Tolerability at site of administration and regarding hemolysis	The company's comments are acknowledged. The section will reviewed and revised accordingly. Regarding point 3, surfactant tolerability is an issue to be addressed by the applicant in the clinical part of the dossier. Therefore, it is not necessary to amend the RP in relation to point 3.
3	We would like to draw the attention of the authority to the fact that	We acknowledge the comments. For all new applications the

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	the discussed surfactants possess anaphylactoidal properties (see references below). Since the reflection is related to safety aspects of surfactants and related parenteral dosage forms, we expect that the authority should point to this issue. As a result, the authority should request a sound justification for selection of these surfactant based formulations for NCE's. In that respect, comparison studies with other solubilizers are mandatory. References: 1. Varma R. K., Kaushal R., Junnarkar A. Y., Thomas G. P., Naidu M. U., Singh P. P., Tripathi R. M.Shridhar D. R. - Polysorbate 80: a pharmacological study. - Arzneimittelforschung, 35, 804-808, 1985. 2. Masini E., Planchenault J., Pezziardi F., Gautier P., Gagnol J. P. - Histamine-releasing properties of Polysorbate 80 in vitro and in vivo: correlation with its hypotensive action in the dog. - Agents Actions, 16, 470-477, 1985. 3. Bowers V. D., Locker S., Ames S., Jennings W., Corry R. J. - The hemodynamic effects of Cremophor-EL. - Transplantation, 51, 847-850, 1991. 4. Eschalier A., Lavarenne J., Burtin C., Renoux M., Chapuy E., Rodriguez M. - Study of histamine release induced by acute administration of antitumor agents in dogs. - Cancer Chemother Pharmacol, 21, 246-250, 1988. 5. Eschalier A., Lavarenne J., Burtin C., Tounissou P. - Acute hemodynamic effects of an antitumoral agent: elliptinium. Involvement of histamine release. - Agents Actions, 17, 441-448, 1986. 6. Ennis M., Lorenz W., Gerland W. - Modulation of histamine release from rat peritoneal mast cells by non-cytotoxic concentrations of the detergents Cremophor El (oxethylated castor oil) and Triton X100. A possible explanation for unexpected adverse drug reactions? - Agents Actions, 18, 235-238, 1986. 7. Ennis M., Lorenz W., Kapp B., Luben L., Schmal A. - Comparison of	toxicological safety of the excipients is a regulatory requirement and should be addressed in the dossier. Given this, it is not considered necessary to amend the RP.

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	the histamine-releasing activity of cremophor E1 and some of its derivatives in two experimental models: the in vivo anaesthetized dog and in vitro rat peritoneal mast cells. - Agents Actions, 16, 265-268, 1985. 8. Lorenz W., Schmal A., Schult H., Lang S., Ohmann C., Weber D., Kapp B., Luben L.Doenicke A. - Histamine release and hypotensive reactions in dogs by solubilizing agents and fatty acids: analysis of various components in cremophor El and development of a compound with reduced toxicity. - Agents Actions, 12, 64-80, 1982. 9. Lorenz W., Reimann H. J., Schmal A., Dormann P., Schwarz B., Neugebauer E.Doenicke A. - Histamine release in dogs by Cremophor E1 and its derivatives: oxethylated oleic acid is the most effective constituent. - Agents Actions, 7, 63-67, 1977.	
4	From Quality point of view: This Reflection Paper is considered a good start and also timely seen the pending discussion at this moment. However, we prefer some editing to improve readability of the Reflection Paper. From non-clinical point of view: The Reflection Paper is meant to indicate when in vivo studies might be needed to support further development and when in vivo studies are not needed. At this moment the Reflection Paper gives some direction. When further experience has been obtained, the Reflection Paper should be supplemented with more information on which bridging studies should be necessary. From PK point of view: The reflection paper has a relatively high level of detail and has more the nature of a guidance, not a reflection paper. However, the	Agree. No revision needed.

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	situation with micelles is extremely complicated especially in case of presence of a different micel forming compound/chemical surfactant in the generic product. The paper properly deals with these complicated situations.	
5	The availability of a reflection paper on the subject of solubilising micellar systems for intravenous administration is highly appreciated. We would recommend focusing on the major risk factors of physical stability solutions during use for surfactant used in this route: **Physical stability** (solubilisation capacity need for preventing precipitation of drug substance) of the surfactant solution upon dilution and refrigeration (paragraphs 3 and 4). This could be regarded as the Design Space of the formulation, its components and the handling instructions. For established surfactants however, additional physico-chemical characterization does not seem to give additional value, in particular as micelles composed of non-polymeric surfactants may cease to exist immediately after dilution in the blood stream. In addition it is known that blood components have a very high solubilization capacity because of presence proteins like serum albumin and lipoproteins. More generally, Sections 2, 3, 4 and 5 describe micellar phenomena relevant to manufacturing, handling, and administration of the product, whereas Section 6 is focused on in vivo behaviour. Sections 2, 3, 4, and 5, are often confusing as they include references to in vivo behaviour. Therefore we suggest adding clarifying statements on the content of Sections 2, 3, 4, and 5 (in vitro studies) and minimize references to in vivo implications as these are better described in Section 6. It is suggested a few times in the proposed reflection paper that the drug containing micelles based on non-polymeric surfactants are not expected to have a very long half-life (e.g. lines 186-192). We think this statement is correct because of scientific considerations (see above) and because lack of any scientific indication in the field of non-polymeric surfactants that the micelles themselves or the drug-surfactant interaction can remain intact for	the recommendation to focus on the risk factors of physical stability solutions during use for surfactant is acknowledged and considered addressed in the revised RP.

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	more than a few seconds upon administration into the venous blood stream. Therefore we see no reason to regard such micellar formulations as “complex parenterals” requiring modelling studies (paragraph 6) or extensive bioequivalence studies (Paragraph 7).	

2. Specific comments on text

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 41-43	1	Caution needs to be exercised in describing surfactants as 'polymeric', and limiting the scope through this definition, as this is not a completely clear boundary. Many small molecule surfactants (including the exemplar Tween 80) contain polyoxyethylene chains as the hydrophile. Thus they share some characteristics of surfactants that are completely polymeric, such as a cloud point, which may be important in development. In addition, some fully polymeric materials (such as the poloxamers) would be considered as candidates for simple solubilized formulations of the type under consideration. These systems together do appear to be distinct from materials in development that have a higher molecular weight and a higher aggregation tendency (e.g. PEG-polylactide and PEG-polycaprolactone). Proposed change It seems more appropriate to limit the scope of the document by reference to the ability to form structures which dissociate rapidly on administration, rather than any specific molecular structural feature of the surfactant.	This comment is partially endorsed and the text has been amended accordingly. We wish to limit the scope to micellar formulations at present although it is acknowledged that it can be extended to other structures which might dissociate rapidly on dilution. Lines 41-42 - it is particularly relevant to ~~'traditional' or 'established' 'small molecule, non-polymeric'~~ surfactants which are sensitive to dilution effects during slow intravenous administration
Lines 36-44	1	We would raise the possibility as to whether	This comment is not endorsed. We wish to limit the scope to

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		cyclodextrins could be brought into scope. Although these do solubilize in a different manner at a molecular level, they share many practical characteristics with micellar formulations. They dissociate rapidly on dilution and their toxicology may be dose-limiting. In the development process they are frequently evaluated alongside surfactants, as they are formulated using similar technology and delivered in a similar way. They share similar failure risks, such as precipitation and mixing sensitivity, limited pH and ionic strength operating range. Proposed change (if any): Consider whether it is appropriate to bring cyclodextrins into scope	micellar formulations at present although it is acknowledged that it can be extended to other structures which might dissociate rapidly on dilution. Although cyclodextrines have a similar behaviour compared to surfactants the characterisation of cyclodextrines will necessarily be different from a surfactant based system. This would involve a major revision of the RP which is currently considered unnecessary.
Lines 45-51	1	We agree that the development of formulations with modified pharmacokinetics or the sophistication of 'targeted' delivery should lie outside these guidelines as such products require special evaluation.	The company's comments are acknowledged. Revision of the RP is not required.
Lines 73-74	1	It is useful to summarize what is known of the drug properties as a technical background. The physicochemical properties of the drug (pH/solubility, pK, partition) are the basis for the development argument justifying a solubilized formulation. In	The company's comments are acknowledged. This comment is endorsed and the text will be revised accordingly.

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		particular the pK of the drug has not been discussed. Drug ionization may limit the formulation pH, such that solubilization is only possible over a limited pH range. The pH may also be manipulated to maximize the chemical stability of the drug substance in the formulation. Data should be available to justify these formulation decisions. This may further require the incorporation of appropriate buffers into the product. Proposed change Include comment that the pK, pH, ionisation, and buffering in the formulation is of importance in determining the overall design of the formulation, and request that the formulator explains the chemical reasoning by which the formulation was justified.	
Lines 102-106	1	It is indeed important to understand the effect of the dilution medium on the C.M.C. of the surfactant as this is likely to be dependent on both pH and ionic strength. In glucose diluents in particular the pH is frequently low. The formulator has the choice of allowing the dilution medium to control the pH, or using a buffer to control pH. In either case the assessment of CMC should be performed in a medium that is aligned with the final use of the product. Proposed change	The company's comments are acknowledged. This comment is endorsed and the text will be revised accordingly.

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		Include a specific reference to controlling both the ionic strength and pH at which the CMC measurements are made.	
Lines 110-114	1	Certain products may be intended for use in hot climates and the stability of both the concentrated formulation, and the diluted infusion solution, should be assessed in as high a temperature as is likely to be experienced in use. This is a particular concern if the surfactant shows a cloud point. Proposed change Replace the suggested temperatures of 15C and 25C with the extrema of temperatures that are likely to be encountered in use, as justified by the product developer.	The company's comments are acknowledged. This comment is endorsed and the text will be revised accordingly. Allow other temperatures to be studied if considered desirable by the Applicant.
Lines 108-114, 137-142	1	We agree that precipitation of diluted solutions during in-use refrigeration is a risk that needs to be considered. Similar arguments also apply to the undiluted formulation. The surfactant may show a Krafft temperature - effectively a precipitation temperature - below which the formulation will fail and this may not be a reversible effect in the short-term. We would also recommend that the risk arising from inadvertent freezing (of both the original formulation and the diluted form) be established. Although it may	The company's comments are acknowledged. This comment is endorsed and the text will be revised accordingly.

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		not be possible to produce a formulation that is robust to freezing, this knowledge would allow label warnings to be used. Proposed change A more robust discussion of the temperature sensitivity of both the undiluted and diluted formulations, taking freezing into account, and with reference to surfactant phase behaviour, would be desirable across Sections 3 and 4.	
Lines 146-159	1	We agree that it is highly desirable to acquire knowledge concerning the molecular physical chemistry of the formulation. However the complexity of the formulations makes this a difficult and often misleading task. Much work in the literature contains errors of method or interpretation. We do not consider dialysis techniques to have any value, for the reasons outlined in the document. Dynamic light scattering may be difficult to perform due to the very small size of the micelles, and is certainly not a routine measurement at this size range. More detailed micelle size information can be acquired by neutron scattering although this is costly and time-consuming. We would normally consider NMR methods as a first line of attack, as this allows the system to be studied noninvasively and can measure free/bound fractions,	The company's comments are acknowledged. This comment is endorsed and the text will be revised accordingly. Text below for consideration: The limitations of the equilibrium dialysis are clearly mentioned in lines 159-164. NMR techniques have been discussed and have been added to the text. Line 164 - ..methodological difficulties. *NMR methods can also be used as it allows the system to be studied noninvasively and can measure free/bound fractions. Diffusion studies can also provide information on the size of the micelles.* Light scattering techniques can be a very useful tool particularly when comparing formulations, e.g., generic vs. reference product. This has been further clarified in the text. Line 158 - …predict how the product will exist in vivo. *Furthermore, it should be clear that absolute quantification of*

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		and obtain size information from linewidth diffusion studies. Fluorescence spectroscopy and energy transfer methods can be useful to establish free-bound equilibria (as mentioned at lines 230-250). We would not normally use zeta potential methods at a micellar scale, as there are many factors influencing this, hindering useful interpretation. Proposed change Add recommendation to use NMR methods and to regard dialysis methods with caution. Point out the difficulties that may be encountered in applying and understanding light scattering techniques for size and surface potential.	*the micelles is not possible using light scattering techniques however a comparison to the reference product is feasible.*
Lines 215-225	1	It is evidently useful to be able to understand the behaviour of the formulation in vivo using in vitro models. The complexity of the biological environment does make it difficult to develop valid biomimetic models and these may well introduce more unknowns that cannot be evaluated. For example, there is little value in adding a lipophilic sink to an in vitro dilution model if it does not have the correct partition and equilibration rate. These will not be known a priori and so the model becomes increasingly difficult to validate as it builds in complexity. We are studying biomimetic systems for in vitro evaluation of parenterals, but this	The company's comments are acknowledged. This comment is endorsed and the text will be reviewed and may be revised.

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		is a long term aspiration rather than a present capability. Current practice would be to take a worst-case approach, such as diluting into a large saline sink, and to couple this with a preclinical evaluation of pharmacokinetics, drug disposition, and local irritancy at the injection site. Proposed change Consider removing any recommendations to develop complex biomimetic models at this stage until the area is better developed.	
Section 7	1	In general we would support the use of the precautionary principle when evaluating generic or similar products. It is easy to lose sight of the complexity of the formulation in the generic landscape, and factors which may appear inconsequential can have an unexpected impact on the formulation safety and efficacy. For 'small' changes ('identical' or 'similar') we would expect to re-evaluate the physical and chemical stability of the formulation, particularly against the formation of particulates, which can appear from unexpected sources (*see stability studies*, below). For more significant formulation changes we agree that evaluation on a case by case basis is desirable. It is not sufficient to claim that surfactants are equivalent	The company's comments are acknowledged. Revision of the RP is not required since the particulates are addressed in Section 4 and it is unclear why the company refers to the use of preservatives for a single use parenteral product.

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		since all micelles dissociate immediately on administration. Solubilized formulations often require significant amounts of surfactant to be administered, which may add complexity to their pharmacokinetics - for example in hepatic or renal function. As a minimum we would expect to perform bridging clinical studies to establish that the formulation pharmacokinetics was similar to that of the innovator product. The use or addition of preservatives as a generic change has not been mentioned. We would welcome opinion on this matter. Presently we would regard the addition of a preservative, even at a low concentration, to constitute a major change to the formulation. Proposed change Specifically mention the need to evaluate quality with respect to particulates and develop guidance as to the inclusion of preservatives.	
Area not considered - Lyophilization	1	The document has not considered the issue of reconstitution of the formulation. Because liquid systems frequently show poor stability that limits their shelf life, lyophilization may be used to convert the formulation to a more stable solid. Although the development of a lyophile formulation is outside the	The company's comments are not endorsed. Considerations regarding lyophilisation are addressed by existing guidelines.

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		present scope, this does raise a number of risks and issues specific to surfactant formulations. 1. When a micellar system is freeze-dried, the micelles may be destroyed, or converted into a more concentrated liquid crystal phase. The fate of the solubilized drug in this process is unclear. It is not inevitable that the system will re-solubilize on dissolution, and the formulator should perform checks to ensure all the drug does go into solution on reconstitution, that particles do not remain, and that the whole process occurs within a clinically acceptable time. 2. Surfactants are frequently soft solids and do not lyophilize well alone. It may be necessary to use a supporting material which may also act as a cryoprotectant for the micelles. The medium for reconstitution should be defined. Ideally the formulation should be robust to reconstitution using any parenteral fluid that is likely to be encountered in a clinical setting. If this is not possible, or if the reconstitution needs a specific diluent, consideration should be given to the provision of a custom diluent, and the use of packaging options and labeling that will reduce the possibility of handling	

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		error. Proposed change Add a further section discussing the considerations for lyophilized formulations, possibly between sections 3 and 4.	
Area not considered - Sterility assurance	1	Sterilization of the formulation has not been discussed. Probably the most significant issue in this regard is that terminal sterilization using moist heat may exceed the surfactant cloud point and damage the formulation. It may be necessary to sterilize the liquid formulation by filtration. Proposed change Include section on sterilization and its impact on quality, possibly between sections 3 and 4	The company's comments are acknowledged. This comment is endorsed and the text will be revised accordingly. (short sentence will be added to ensure that CPP on product quality to be addressed)
Area not considered - stability studies	1	It will be necessary to present data to show that the product is chemically and physically stable over its lifetime and in-use form. This has been touched on in Section 4 but some additional comments may be helpful. The use of standard stability protocols and ICH storage guidelines will be a basis for the development of the pivotal stability data. During development, accelerated (e.g. high temperature) stability methods will be found to be of limited value	The company's comments are acknowledged. This comment is endorsed and the text will be revised accordingly.

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		due to the various temperature-dependent properties of the surfactant. The chemical stability of the drug may be usefully improved when in micellar solution, and in such circumstances it may be possible to combine chemical kinetics and surface chemistry data to create predictive models of chemical stability. These can be useful in formulation development and further in the establishment of a quality by design strategy. The most significant physical stability issue is likely to be the formation of solid particulates. These can appear gradually from unexpected sources - for example hydrolysis products of the drug or minor components of the surfactant. The identification and mitigation of these may be a significant development issue. Older particle counting techniques that are adequate for quality assessment may not provide sufficiently detailed data for development purposes. Without wishing to endorse specific instruments, we have found the most recent generation of light blockage and scattering particle counters, which resolve particles of 1 micrometre and provide a complete particle size distribution, to be invaluable for this purpose. Proposed change	

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		In section 4, increase emphasis on the need for real-time stability data, the difficulty of applying accelerated stability methods, and the need to monitor particle generation as a particularly important quality indicator. In general it does seem that there is an omitted section in the document, in that stability issues in the undiluted formulation have not been extensively discussed.	
Area not considered - Toxicology	1	The document makes little mention of the toxicology of the surfactant. In our experience the amount of drug that can be administered is frequently limited by the need to avoid a toxicological reaction to the surfactant. Proposed change Include specific comment that the toxicology of the solubilizer should be considered when determining the concentrations for use in both preclinical and clinical testing.	The company's comments are acknowledged. For all new applications the toxicological safety of the excipients is a regulatory requirement and should be addressed in the dossier. Given this, it is not considered necessary to amend the RP.
Line 32ff:	2	It is recommended to clearly define the scope and not to refer to delivery systems which are explicitly out of scope and are indeed expected to behave differently in vivo (polymeric micelles).	The company's comments are acknowledged. The section will reviewed and revised accordingly.
Line 41ff:	2	It is mentioned that the text applies in particular to "traditional", "established", non-polymeric surfactants like Tween80, which are sensitive to dilution effects during slow i.v. infusion. It is not clear how what	This comment is endorsed and the text has been amended accordingly. We wish to limit the scope to micellar formulations at present although it is acknowledged that it

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		traditional or established means. Does this exclude novel surfactants even if they are non-polymeric? It would be possible to give a positive list of established surfactants for the route of administration or refer to review papers on solubilizing excipients by Strickley, Nema etc.	can be extended to other structures which might dissociate rapidly on dilution. Lines 41-42 - it is particularly relevant to ~~'traditional' or 'established' 'small molecule, non-polymeric'~~ surfactants which are sensitive to dilution effects during slow intravenous administration
Lines144-169	2	i) Physical stability (solubilisation capacity need for preventing precipitation of drug substance) of the surfactant solution upon dilution and refrigeration (paragraphs 3 and 4). This could be regarded as the Design Space of the formulation, its components and the handling instructions. For established surfactants however, additional physico-chemical characterization does not seem to give additional value, in particular as micelles composed of non-polymeric surfactants may cease to exist immediately after dilution in the blood stream. In addition it is known that blood components have a very high solubilization capacity because of presence proteins like serum albumin and lipoproteins. The pharmaceutical relevance of the considerations in paragraph 5 is not obvious.	The company's comments are acknowledged nevertheless it is considered important that empirical data is provided even for well established excipients to support the product design and expected bioavailability.
Lines144-169	2	ii) Compatibility with injection/infusion devices A major risk factor, which is not mentioned in the draft, is the assessment of the compatibility of the micellar formulations with infusion materials as surfactant based formulations have, by their nature, a high tendency to extract plasticizers and to adsorb to	The company's comments are acknowledged. The section will reviewed and revised accordingly.

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		surfaces.	
Lines144-169	2	iii) Tolerability In case novel surfactants are deployed, a thorough physico-chemical characterization (CMC, effects of polydispersity) and toxicological evaluation, should be performed. Required tests for local tolerability and hemolytic effects of the surfactant system at the site of injection should be described in the reflection paper.	The company's comments are acknowledged. The section will reviewed and revised accordingly. However, it is not considered necessary to specify test methods.
186-192	2	More generally, it is suggested a few times in the proposed reflection paper that the drug containing micelles based on non-polymeric surfactants are not expected to have a very long half-life (e.g. lines 186-192). We think this statement is correct because of scientific considerations (see above) and because lack of any scientific indication in the field of non-polymeric surfactants that the micelles themselves or the drug-surfactant interaction can remain intact for more than a few seconds upon administration into the venous blood stream. Therefore we see no reason to regard such micellar formulations as "complex parenterals" requiring modelling studies (paragraph 6) or extensive bioequivalence studies (Paragraph 7).	The company's comments are acknowledged. The section will reviewed and may be revised accordingly. The extent of data provided should reflect the novelty of the formulation.
Lines 41-51	4	It may be helpful for the reader to provide examples of excipients which may be relevant in the context of this reflection paper, e.g., polymeric and non-polymeric surfactants like polysorbate 80 and Cremophor, complexing agents like cyclodextrins, and fatty acids.	Noted. However, the scope of the RP has been revised to exclude complexing agents and to delete reference to polymeric and non-polymeric surfactants.

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Line 54	4	Please note that solubilsed should be solubilised	Text amended.
Lines 91-92	4	It may be helpful for the reader to add a glossary (e.g. clarifying (differences between) polydisperse and heterodisperse).	Not considered necessary for a RP.
Section 6	4	This paragraph would gain clarity when a more systematic approach would be followed. As the reflection paper is meant to define conditions whether or not in vivo studies are needed, this could be made clearer in the text. In addition, it could be made clearer which data can be derived from literature.	This section has been revised in light of other similar comments.
Lines 226-248	4	This part is meant to describe the modelling systems that can be used instead on in vivo studies. The paragraph is a mix of a review and recommendations. We suggest making this clearer.	Minor revision has been undertaken, but the text is considered adequate for a RP.
Line 281	4	It is preferred to replace 'questioned' by 'considered'.	On review "questioned" has been replaced by "called into question"
Line 287-288	4	We propose to add some examples of in vitro studies that could be useful.	The text already refers to other RP sections where examples are given.
Line 32 ff	5	It is recommended to clearly define the scope of the document and is suggested therefore that a positive list of surfactants pertinent to this reflection paper, and for the route of administration, be provided. Additionally, clearly defining those products which are out of scope e.g. liposomal products would also provide clarification.	The comment is acknowledged. Scope of the RP has been revised and made more specific such that a list of surfactants is not considered necessary and by implication omits liposomal products from the scope. The scope clearly states that the RP applies to drug products administered intravenously.
Lines 41-44	5	In addition to the comment above, it is mentioned that the text applies in particular to "traditional", "established", non-polymeric surfactants, which are sensitive to dilution effects during slow i.v. infusion. It is not clear what traditional or established means. Additionally, given the only example provided of a "non-polymeric surfactant" is polysorbate 80, for which	The comment is acknowledged. Reference to the terms "non-polymeric", "traditional and established" have been deleted.

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		it is not clear why this qualifies as “non-polymeric. It is therefore recommended that a definition is needed for the term “non-polymeric” surfactants and clarification be provided as to whether novel surfactants would be excluded even if they are non-polymeric. Additionally, please clarify the criterion for “slow intravenous administration”. For example, is an infusion time of one hour considered to be slow?	The text has been amended to take account of this comment.
Line 45	5	It is recommended that the text keeps to the scope i.e. non-polymeric and does not to discuss delivery systems (e.g. polymeric, lines 45-51) which are explicitly out of scope and are indeed expected to behave differently in vivo.	The comment is partially endorsed. Since polymeric surfactant systems can also be characterised by the tests described in the RP, reference to these systems is appropriate. But it is acknowledged that additional tests may be required taking such product out of scope of this RP.
Lines 80-81	5	**Editorial comment:** Please consider using the acronym “c.m.c.” rather than “cmc” for critical micelle concentration in order to avoid confusion with the common abbreviation of CMC for “chemistry, manufacturing and controls”.	The comment is acknowledged. The text will be revised.
Line 95	5	**Comment:** As Reference 5 (book published in 1967) is not readily available, please consider to either eliminate Reference 5 or replace with a more retrievable reference.	Reference has been deleted.
Lines 72-106 Sections 1 & 2	5	**Comment:** These two sections contain a description of how to characterise the surfactant behaviour and content, e.g., in line 76 quality parameters are mentioned. Excipient manufacturers obtain their surfactants from different sources and normally protect their recipe, hence surfactant polydispersity and purity can not always be obtained. **Proposed change:**	The comment is acknowledged. The text has been revised to focus on those excipients attributes affecting the drug product performance and safety. If the applicant is able to define the critical quality parameters that affect the performance of the surfactant system, detailed information on the surfactant polydispersity and purity might not be required.

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		We would suggest an alternative approach consisting in defining relevant quality parameters to ensure the performance of the used surfactants and letting the companies define that them-selves based upon their knowledge about the formulation and the critical parameters, which the formulation work has revealed.	
Lines 79-106	5	**Comment:** The requirement to determine c.m.c. is a relevant parameter to describe the system, however the c.m.c. for polysorbate or cremophor has been measured numerous times, hence this point only seems relevant when new excipients or combinations are used. Furthermore, the suggested measurement methods may not be sufficiently precise to determine very low c.m.c. values. Determination of c.m.c. in saline is relevant for ionic surfactants, whereas non-ionic surfactants should be unaffected. **Proposed change:** We would suggest changing the wording so it is suggested to investigate c.m.c. while acknowledging the scientific difficulties in the experiment in the above mentioned instances.	The comment is not endorsed. It is considered important that relevant data for this critical attribute of the applicant's drug product is provided to show consistency with established scientific knowledge.
Lines 107-112	5	**Comment:** The section describes the solubilisation capacity and defines a temperature range from 15-25°C. Two parameters are affected by the temperature for systems with non-ionic surfactants i) the solubility of the compound and ii) the hydrophilic affinity of the surfactant. Additionally, the prescribed usage and storage conditions may also include refrigerated conditions and, to accommodate global product development, experiments may also be conducted at	The comment is acknowledged. The text will be revised.

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		30°C. It may therefore be relevant to expand the range to **under selected conditions of use.** **Proposed wording:** Micellar media relevant to infusion solutions should be challenged by incorporating increasing concentrations of drug and noting the point at which phase separation occurs at 15C and 25C under selected conditions of use. This gives an indication of how great is the margin of safety before the crystallisation of the drug becomes a possible danger for the patient.	
Lines 112-114	5	**Comment:** More appropriate wording is needed than references to 'cold' and 'warm' hospital environment. For instance, it is standard practice to investigate quality parameters during different conditions of use of the product. **Proposed change**: "This gives an indication of how great is the margin of safety before the crystallisation of the drug becomes a possible danger for the patient, ~~taking into account a "cold" and "warm" hospital environment~~ ***ensuring that in-use studies, encompassing the temperature ranges encountered in hospital settings, address temperature effects on micellar behaviour***."	The comment is acknowledged. The text will be revised.
Lines 119 – 124	5	**Major comment:** We propose that this paragraph be re-worded, and the following statement deleted: "The recommendation of an intravenous in-line filter to remove precipitated drug arising from a badly-developed product with no	The comment is acknowledged. The text will be revised.

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		margin of safety represents bad practice". The sponsor will provide evidence that supports the stability of their products when handled as prescribed. However, as products are prepared in a hospital setting, over which the sponsor has no control, the use of an in line filter could be acceptable as a precaution in order to maintain physical stability and/ or sterility during the preparation of the infusion solution. **Proposed changes:** ~~"The recommendation of an intravenous in-line filter to remove precipitated drug arising from a badly-developed product with no margin of safety represents bad practice~~. It should be demonstrated that the pharmaceutical development leads to a robust product with the drug in solution and the selected storage conditions and shelf-life of the infusion solution should include a margin of safety with respect to the occurrence of drug precipitation. Thus, under normal/label recommended conditions of use, the infusion solution is not expected to precipitate. Nevertheless, as a general principle of precaution, an in-line filter may be recommended".	
Line 125	5	**Major comment:** We propose that the following additional text is added as an introduction to Section 4 : "The stability of a micellar solution can be impacted by	The comment is acknowledged. The text will be revised.

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		different factors (eg temperature, agitation). For this reason the impact of these factors on the characteristics of these micellar solutions should be comprehensively evaluated".	
Lines 128-130	5	**Comment:** As for the comments for Line 112-114, more appropriate wording is needed than references to 'cold' and 'warm' hospital environment.	The comment is acknowledged. The text will be revised.
Lines 137-142	5	**Major comment:** We propose to modify the text to: The effect of temperature on these complex systems is difficult to predict. It has been observed that for certain micellar systems, refrigerated conditions did prolong the physical metastability. Therefore, in order to further assist users, the ability of the diluted product to resist phase separation, under the selected usage and storage conditions, should be investigated to see what is the margin of safety in this regard, given the realities of clinical and pharmaceutical practice. The retained storage conditions should derive from the performed studies. **Reason for comment:** The statement that "but it is likely that refrigeration will lead to precipitation of the poorly-soluble drug" is contrary to sponsor's drug.	The comment is acknowledged. The text will be revised.
Lines 144-169 Section 5	5	As micelles composed of non-polymeric surfactants may cease to exist immediately after dilution in the bplood stream, of the product upon injection, the	The comments are acknowledged nevertheless it is considered important that empirical data is provided even for well established excipients to support the product design and any

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		pharmaceutical relevance of the considerations in paragraph 5 is not obvious.	biowaver.
Lines 144-169 Section 5	5	**Comment:** The section contains a number of characterisations of the formulation. Measurement of particle size is relevant for IV injection and should be suggested, however, in real micellar systems, this should not be a critical factor – and the same thing goes for zeta-potential in systems with non-ionic surfactants. Additionally, it is not clear why measurement of free versus solubilised fractions is required, as the use of the information is not clear. Also, determination of the free fraction in experimentation is very difficult as all measurement methods will affect the equilibrium. It could, with a number of reservations, be conducted by dialysis as suggested in line 160, but this is not always a straight forward investigation. Other methods may be used as well, including ACE and ITC, but again the experimental design is difficult. We suggest that literature references are added for all cited analytical methods. **Proposed change:** **Please revise the text of the reflection paper to acknowledge the above considerations – or simply omit the section.**	The comment is acknowledged. The text has been revised. With respect to determination of free drug, an explanation has been provided as to its value, but the text already acknowledges the technical difficulties.
Footnote 10 (Bottom of page 6)	5	**Comment** : Please see proposed modification to footnote 10 **Proposed change :** In case of inconclusive in vitro results or when results indicate a risk of persistence of the micellar system in vivo, such models should be supported in Modules 4 & 5 of the CTD by in vivo pharmacokinetic studies, possibly in animals but preferably in humans, showing	The comment is acknowledged. The text will be revised accordingly and moved to the main body of the RP.

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		entrapped/free drug levels and the fate of the micellar component. It is essential that these pharmacokinetic studies are undertaken within the correct time frame. In cases where micellar systems with entrapped drug are found to also persist in vivo it may be necessary to also present data on biodistribution (% dose) and not just classical kinetic parameters. Tissue distribution of drug will then influence efficacy/safety and guide preclinical toxicological and clinical studies/protocols.	
Lines 170-260 Section 6	5	**Comment:** This section is highly theoretical and academic. The cited literature in the section describes micellar disruption *in vivo*, however : (1) the cited studies were done with polymeric surfactants and the extrapolation to non-polymeric surfactants is not justified scientifically and (2) the citations appear to represent isolated studies without subsequent confirmation by other researchers.	The RP is attempting to develop understanding in this matter. Reference to non-polymeric and polymeric surfactants has been deleted. Please note that the scope of the RP has been revised in light of other similar comments.
Lines 170-260 Section 6	5	**Comment:** This section contains a number of statements, starting line 216 and throughout the section, which do not necessarily reflect the current knowledge. These are scientific suggestions with an unknown scientific value as the methods are not well-described. For example, the required “careful validation” of the methods (line 258), does not reflect the current scientific knowledge. **Proposed change:** Please consider omitting the statements referred to above. An alternative approach is to let companies define their own scientific fundaments and justify them.	The RP is attempting to develop understanding in this matter. Reference to non-polymeric and polymeric surfactants has been deleted. Please note that the scope of the RP has been revised in light of other similar comments.
Lines 188-	5	**Major comment:**	The comment is acknowledged. The text will be revised

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192		The use of the word “likely” in the sentence starting on line 189 suggests that itis a frequent observation that the micelle component is much more transient in vivo than may be imangined, yet is not consistent with the sponsor’s drug. Therefore it is suggested to start the sentence: “It is possible that this observation....” or “It could be that this observation.....”	accordingly.
Line 199; point 2	5	**Major comment:** **P**lease include the following additional text: The surfactant may be involved in interactions with proteins.	The comment is acknowledged. The text will be revised accordingly.
Lines 213 - 214	5	**Comment:** g No data are referenced to substantiate this statement. **Proposed change**: “~~Equilibrium 5 is more rapid, and is probably what happens to most lipophilic water insoluble drugs released from micelles in any case.~~”	Although no reference has been included, the comment is not endorsed taking account of current pharmacokinetic knowledge.
Line 233	5	We caution the use of fluorescent dyes as a way to investigate micelle properties. Given that the physical and chemical properties of these dyes are different from the studied drug (eg partition coefficient, kinetics of phase equilibrium, etc), it may lead to a significantly different structure and behavior of the micellar system. Therefore, the observed results will not necessarily apply to the studied drug. Consider other first intent options, such as use of radiolabelled materials as it is proposed at the end of the section (lines 249 - 250).	The comment is not endorsed because section 6 describes different modelling studies but it doesn’t prioritise a particular method.
Line 226	5	**Comment**: No reference/justification is provided to support the chosen volume of 3 litres, therefore we suggest that a reference or justification is provided	The comment is acknowledged. The text will be revised accordingly.

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Lines 249 – 253	5	**Comment:** Text is identical to footnote 13, therefore suggest to reword or remove footnote 13.	The comment is acknowledged. Footnote 13 has been deleted
Lines 253 - 254	5	**Comment**: No data are referenced to substantiate the statement "It is likely this also happens with non-polymeric surfactant micelles" therefore we propose it is removed.	The comment is acknowledged. The text will be revised accordingly.
Line 269	5	**Comment:** The term "bioavailability" is inappropriate, therefore we propose the following change: "What is the likely effect of formulation/manufacturing changes on ~~bioavailability~~ ***biodistribution and/or pharmacokinetics***?"	The comment is acknowledged. The text will be revised accordingly.
Line 270	5	**Comment:** Variation in the results for some of the bioequivalence surrogate markers detailed in Sections 1 to 6 should be permitted, on proviso that it has been demonstrated that such variability is negligible clinically. **Proposed change :** Please add the following statement (new paragraph after line 270): "Any differences in the results for the surrogate markers of bioequivalence between the current and proposed product should be justified, and where possible, its relevance to the clinical setting should be discussed".	The comment is acknowledged. The text (section 7) will be revised accordingly.
Lines 318-323	5	**Major comment:** The addition of small amount of citric acid to the sponsor's investigational products containing polysorbate 80 have increased the toxicity of the compound in animal species. The explanation of	The comment is acknowledged. The text has been revised to include the potential for safety implications of differences in excipients composition.

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		these findings is still unclear. Therefore we suggest to include the following additional text to the end of bullet 1 : “Addition of small amount of citric acid may lead to modify the toxicity profile of the compound and therefore it is recommended to perform at least non clinical studies to support a biowaiver”	
Line 324	5	**Comment:** Products containing PEG or other excipients should be in the category listed under 7.1.4 Different Formulations (line 338)	The comment is not endorsed since the text explains that excipients present in very small amounts are unlikely to affect the micellar solution.
Lines 349-350	5	**Major comment:** There are ample references in the literature to support the conclusion that these “different formulations” should be required to demonstrate "therapeutic equivalence" in patients based on both pharmacokinetic and “clinical safety” profiles after repeated administration. Therefore we suggest to include the following additional text at line 350 : “[...] confirming safety, if necessary. In most cases, these “different formulations” would most likely be required to demonstrate "therapeutic equivalence" in patients based on both pharmacokinetic and clinical safety” profiles after repeated administration. “ It is suggested that the following is added as a footnote: “Docetaxel formulations that omit or alter the concentration of PS80 could have a significant effect on certain cumulative toxicities. For example, severe fluid retention has been reported following treatment	The comment is not endorsed because this is a RP about pharmaceutical development not a clinical document. The document states that using different formulations additional non-clinical and clinical studies may be necessary.

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		with Taxotere.**Error! Hyperlink reference not valid.** In one study, for example, among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%.**Error! Hyperlink reference not valid.** Fluid retention is a complicated and unpredictable toxicity. For example, it appears to be a cumulative dose toxicity as it has not been observed in single dose human studies. In the repeat dose study mentioned above, the median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m^2. In addition, fluid retention appears not to be explained by either docetaxel or PS80 alone, but rather through the interaction of the two components of the formulation. For example, Vepesid® (etoposide formulated with PS80) does not cause fluid retention in man.**Error! Hyperlink reference not valid.** Similarly, the intensity of fluid retention appears less marked even without premedication in patients treated with an investigative liposomal formulation of docetaxel that does not contain PS80 compared to that observed with premedication with the standard Taxotere. Finally, fluid retention was not observed in animal species used in nonclinical safety studies.**Error! Hyperlink reference not valid.** As a result, there is currently no animal model to study the mechanism of fluid retention. **Error! Hyperlink reference not valid.** Taxotere PI. **Error! Hyperlink reference not valid.** id. **Error! Hyperlink reference not valid.** Vepesid	

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		Prescribing Info., available at, http://packageinserts.bms.com/pi/pi_vepesid.pdf. **Error! Hyperlink reference not valid.** Data on file with sponsor. The only adverse effect resembling this change and noted during the course of animal studies was persistent ear thickening noted in dogs. This was noted only after several cycles at 1.5 mg/kg.	
Line 97	5	Editorial comment Proposed change (if any): Add bullet point before "surface tension[6]"	The comment is acknowledged. The text will be revised accordingly.
Line 127	5	Editorial comment: "Confirm" and "confirmed" in same line Proposed change (if any): Delete "the principle of the MAC is confirmed and" [..].	The comment is acknowledged. The text will be revised accordingly.
Line 140	5	Editorial comment Proposed change (if any): Replace "see what" with "establish".	The comment is acknowledged. The text will be revised accordingly.