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Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems

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Scope

This paper describes a basic package of information which could be relevant to confirm the sound pharmaceutical development and full characterisation of products of this type.

In particular, this text applies in the following context:

- medicinal products for intravenous injection or infusion that contain active substances, which have a low aqueous solubility and which are formulated in an aqueous surfactant micellar system[1], where the main objective of the development is to solubilise the drug, and not to create a system where special size- or surface-dependent properties of the disperse phase are critical factors in the kinetics and disposition of the drug;
- the micellar solubilisation of interest is characterised by the aqueous solubility of the active substance remaining very low until the surfactant concentration reaches the critical micelle concentration (c.m.c.). At surfactant concentrations above the c.m.c., the solubility of the active substance increases in proportion with the concentration of the surfactant, indicating that solubilisation is related to the presence of micelles.[1A];
- it is particularly relevant to surfactants that are sensitive to dilution effects during intravenous infusion, are rapidly metabolised and which therefore do not have a long half-life in plasma, e.g. polysorbate 80.

Additional considerations would apply to certain polymeric surfactant systems developed to create a 'delivery system' in addition to a solubilising system and which have special properties affecting kinetics and distribution *in vivo*, e.g. very low critical micelle concentration (c.m.c.) or prolonged half-life[2] (e.g. innovative block co-polymer surfactants) or to those oncology products designed to utilise the EPR effect[3] (Enhanced Permeability and Retention). Such systems *may* be characterised in part by the tests described in this RP, but as it is likely that additional studies would be needed, these products are not considered within the scope of this RP.

In micellar solutions, there exists, in rapid dynamic equilibrium, different species of the drug substance (as aqueous solute or drug substance solubilised in the micelle) and surfactant (as monomer or in micellar form). In this way, precipitation of the drug substance is avoided. These drug products are normally presented as stable sterile concentrates (e.g. powder and solvent for concentrate solution for infusion, concentrate and solvent for solution for infusion, concentrate for solution for infusion).

The micellar solution is normally prepared for intravenous infusion by dilution with a large volume of aqueous 0.9% sodium chloride or 5% dextrose injection.

On intravenous infusion of the products described by the bullet points above, the dispersed micelles are broken down if subjected to appropriate dilutions (i.e. to below the c.m.c.), such that the drug substance is presented to the blood compartment in a 'free' rather than 'solubilised' form. Nevertheless, it should be acknowledged that these are generalisations and that the specific qualities and attributes of both the drug substance and micellar formulation excipients need to be specifically considered on a case by case basis.

Given the complexity of micelle systems, a comprehensive pharmaceutical development is necessary, needing an understanding of what happens to the product after administration, including an assessment of the risk of precipitation as a function of the rate of administration. It is acknowledged

1 Hoiland H and Blokhus M : Solubilisation in aqueous surfactant systems, in Birdi KS Handbook of Surface and Colloid Chemistry, CRCPress, 1997

1A Rangel-Yagui et al., Micellar solubilisation of drugs, J Pharm Pharmaceut Sci , 8(2), 147-163, 2005

2 Matsumura Y : Polymeric micellar delivery systems in oncology, Jpn J Clin Oncol. 38(12), 793-802, Dec 2008

3 Duncan, R. (2006) Polymer conjugates as anticancer nanomedicines. Nature Reviews Cancer, 6, 688-701

that this development may involve some tests that are not currently well-reported, and applicants are encouraged to develop and validate such techniques for themselves, particularly those which give information on the likely state of these systems *in vivo.* Therefore, applicants are advised to discuss the pharmaceutical development with the regulatory authorities and/or to seek Scientific Advice from the CHMP.

1. Properties of the medicinal product ingredients

The lipophilicity and solubility of the drug substance should be fully characterised, and the known *in vivo* disposition should be described. Data for the drug substance such as pKa, pH-solubility, pH-partition coefficient and pH-stability profiles are useful information for the pharmaceutical development of a micellar solubilization system.

Each excipient should be described and its function fully justified. Relevant critical quality parameters affecting drug product performance and safety should be described and justified. Physico-chemical characterisation, surfactant polydispersity and purity should be considered. Taking into account that different types of surfactants (non-ionicvs anionic and cationic surfactants) can be used, the relevance of the pH and the ionic strength in the design of the formulation should be discussed.

The proposed pharmaceutical form should also be justified and the point at which the micellar solution is prepared for administration should be fully described.

2. The critical micelle concentration (c.m.c.) of the surfactant

To begin with, it is useful to know the critical micelle concentration (c.m.c.) of the surfactant used[4]. Calculations based on the c.m.c. are useful to indicate that a micellar component is *likely* to be present to solubilise the drug substance.

For single molecular mass surfactants, the c.m.c. depends upon the structure and purity, and in particular the characteristics which determine surface activity must be controlled – e.g. the alkyl chain length of the lipophilic region and the characteristics of the hydrophilic region e.g. polyoxyethylene chain length, although this latter does not have such a great effect as the former on the c.m.c. of most non-ionic surfactants.

There are several definitions of the c.m.c., but for the purposes of this paper it may be taken to represent the maximum limit of solubility of the (monomeric) surfactant in the bulk solvent, at the point where self-assembly into micellar structures begins. Given the variability in composition of industrially manufactured surfactants, many of them may be classified as *polydisperse*, and the c.m.c may be expected to vary from batch to batch. However, in contrast to monodisperse systems, their solubilising properties may be expected to be close to that of an equivalent monodisperse compound having a chemical formula of the mean. Therefore, while pure surfactants are normally required for physical chemical studies, useful information may still be obtained from solutions of polydisperse materials of this type.[5]

A wide range of techniques are described for the measurement of c.m.c., for example:

- surface tension[6];

4 Hiemenz, P: Principles of Colloid and Surface Chemistry, CRC Press, 1997

5 Paul Becher, in 'Nonionic Surfactants' , ed. M.J Schick, Surfactant Science Series Vol. 1, Ch 15, Marcel Dekker Inc., New York, (1967)

6 Cosgrove T, 'Colloid Science: Theory, Methods and Applications'. Wiley Blackwell, 2005

- light scattering[7];
- dye solubilisation[8];
- conductivity (but since the majority of surfactants for clinical use are probably nonionic in nature, conductivity methods may not be so useful).

The c.m.c. of a surfactant may vary depending on the composition of the solution in which it is dissolved, therefore the media chosen for measurement should be as close as possible to the composition of any diluted solutions immediately prior to infusion. The ionic strength and pH of the solution in which the c.m.c. measurement are made should be considered.

It cannot be assumed that the c.m.c. in water or saline is the same as the c.m.c. in plasma, so the c.m.c. should be recorded for information only, to indicate the presence of the micellar component prior to infusion of the product.

3. Solubilising Capacity

Given the presence of any micellar system, it is useful to know its 'capacity' to solubilise the active substance. The Maximum Additive Concentration (MAC) or other similar attribute provides this assurance with regard to the active substance as the additive in question.

Taking into account that temperature has a relevant impact on micellar solubilisation, 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 the extremes of temperature that are likely to be encountered in 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. In-use studies, encompassing the temperature ranges encountered in hospital settings, should address temperature effects on micellar behaviour.

The MAC is linked to the concept of 'cargo capacity' which is a feature of novel drug delivery systems, especially those based on micellar or liposomal systems. New surfactants are being developed for pharmaceutical applications having a greatly increased cargo capacity for water-insoluble drugs, and a prolonged half-life *in vivo*.

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.

4. Physical stability and compatibility of diluted infusion solutions

The preparation of the diluted infusion solution should be fully described and justified. Critical steps in the preparation should be verified.

The micellar formulations show a remarkable sensitivity to temperature. If the c.m.c. is an important property of surfactants, as commented before, another relevant characteristic is the Krafft temperature. This can be defined as the minimum temperature at which surfactants form micelles.

7 Mazer N A, Laser Light Scattering in Micellar systems in 'Dynamic Light Scattering: Applications' by R Pecora, Springer 1985

8 Das A K, Hajra A K , J Biol Chem, 267 (14) 9731 (1992) http://www.jbc.org/cgi/reprint/267/14/9731.pdf

Below that temperature the formulation will fail because the surfactant remains in crystalline form, even in aqueous solution. On the other hand, as highlighted above, temperature can have a relevant effect on MAC.

Taking into account the principles mentioned above, in addition to the normal in-use stability studies, it is useful to confirm that drug crystallisation does not occur over a time interval relevant to the preparation and administration process and at the temperatures likely to be encountered in use. Diluted product at the extremes of the range of concentrations likely to be encountered in clinical practice should be used. Given the complexity of these systems, this study should be conducted using diluted infusion solutions prepared from undiluted samples during its shelf-life

Applicants should pay particular attention to the wording in the current guideline on maximum shelf life of sterile products after first opening (CPMP/QWP/159/96 corr):

"… from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 – 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions…"

The effect of temperature on these complex systems is difficult to predict. It has been observed that for certain micellar systems, refrigerated conditions prolong the physical metastability. Therefore, in order to further assist users, the resistance of the diluted product to phase separation if refrigerated after dilution but prior to infusion should be investigated, to determine the margin of safety in this regard. It may be necessary for the product literature to specifically advise against refrigeration. The effect of freezing on these formulations should be studied. Risks arising from inadvertent freezing, if any, should be stated in the SPC and package leaflet.

Compatibility with injection and infusion devices

Taking into account that the surfactant based formulations have, by their nature, a high tendency to extract plasticizers from bags and infusion sets used routinely in clinical practice9, as well as to adsorb to surfaces, the compatibility of the micellar formulation with injection and infusion devices should be discussed in detail.

9 Hennenfent KL, Govidan R. Novel formulations of taxanes: A review. Old wine in a new bottle?. Ann Oncol 2006 May; 17(5):735-749

5. Characteristics of the micelle component & free drug fraction prior to administration

It is useful to know the important characteristics of the micelle component in solutions immediately prior to injection/infusion according to the dilution/administration instructions in the SPC, in particular:

- mean size and size distribution of the dispersed micellar component
- estimated concentration of micellar entities, reflecting the extent (amount) of the micellar component.
- [free] vs [solubilised] fractions of the active substance

Dynamic Laser light scattering is often the most commonly used method to give information on size and extent of any micellar component which may be present. However, it is important to keep in mind that light scattering techniques may be difficult to perform because of the very small size of the

micelles. Nevertheless, although an absolute quantification of the micelles is not possible using these techniques, comparison between the generic and the reference medicinal product is feasible.

The resulting fluorescence arising from a fluorescent probe by dye solubilisation may be used to give an indication of the extent of any micellar component which may be present, normally a function of how much surfactant is present and its c.m.c.. Again, since it cannot be assumed that the micellar properties prior to infusion are the same as the micellar state *in vivo*, this information should be used only to indicate the 'pharmaceutical' state of the product prior to infusion. It should not be used to predict how the product will exist *in vivo.*

The amount of free drug should be significantly below the saturated solubility of the drug substance in the infusion solution and if determined provides further evidence of drug product suitability.

NMR methods can be used because these allow the system to be studied non-invasively and can measure free/bound fractions. Diffusion studies can also provide information on the size of the micelles. Equilibrium dialysis[9] can also be used. However, since in most cases the drug will have a very low aqueous solubility, the free drug concentration is expected to be very low since the partitioning equilibrium is in favour of the micelle interior. Furthermore, the possibility of surfactant monomer crossing the membrane and re-assembling should be kept in mind, as this can introduce further methodological difficulties.

In certain cases, depending on the claims made by the applicant, it could be relevant to describe knowledge of the surface characteristics e.g. surface charge as reflected in the zeta-potential, although this would probably not be a standard requirement for micelles with a very short half-life *in vivo*. Concerning the test methods mentioned above, any other relevant and justified validated methods could be considered.

6. Modelling studies indicating the persistence and extent of the micelle component *in vivo*

Normally, micellar parenteral drug products are administered by intravenous infusion, and are therefore subject to dilution effects which may promote the breakdown of the micellar component, with the rate of infusion sufficiently low to minimise the risk of precipitation of the active substance *in vivo*.

The method and rate of administration may affect the disposition of the drug substance and drug product excipients. (Note that this may not necessarily be the case with a rapid or bolus intravenous injection, where rapid breakdown of the micellar component may not occur to the same extent). The clinical dossier should justify the time and conditions of the infusion process, taking into account such issues as potential haemolysis, CNS effects, etc.

As an extended aspect of the pharmaceutical development of these complex systems, it is essential to gather as much information as possible concerning what is likely to happen to the drug and the micelle component *in vivo*. In general, the 'persistence' and extent of the micelle component are probably of more interest than the size or electrostatic properties for small molecule surfactants. It is possible that micelles will disappear during a slow infusion, simply due to dilution and metabolism of the surfactant, but applicants should consider the number of competing equilibria to arrive at a better understanding of what is happening.

9 Smith G A and others, Use of the semi-equilibrium dialysis method in studying the thermodynamics of solubilization of organic compounds in surfactant micelles. J Solution Chemistry, 15, 6, (1986).

In this regard, the overall picture emerging from the recent literature is that the micellar component is highly transient *in vivo* and evidence points to rapid loss of micelle integrity and dispersal of the 'free' drug systemically.

Nevertheless, as a point of departure it is useful to consider the mechanisms in the human body acting on intravenous lipophilic drugs solubilised in micelles and the associated risks. The following should be considered:

1. Initially, the micelle component disappears because of simple dilution below the c.m.c. of the surfactant[10], and the drug is released. Theoretically, micelles may re-form as more product is infused, and this equilibrium is in competition with 2. below;
2. Surfactant monomer may be exposed to metabolic clearance by plasma enzymes as well as to interactions with proteins[11]. This leads to a re-adjustment of the micelle -> monomer equilibrium, accelerating the breakdown of the micelles and release of 'free' drug;
3. The free drug may bind to plasma proteins, or may otherwise be 'transferred' out of the micellar system. If the affinity for plasma protein or other in vivo lipophilic domain is greater than the affinity for the micelle interior, then the drug will be depleted from the micellar component, even though the latter may persist in vivo;
4. The free drug may be sufficiently and rapidly diluted to be present as a solute;
5. Free drug may partition itself into the many lipophilic domains in the body;
6. The free drug may precipitate upon administration, particularly if administered rapidly. This is considered a major safety concern.

In the *in vitro* modelling of the administration process in human plasma, the first three of the above mechanisms are retained, but 4 & 5 are not. Equilibration into total body water is probably slow, and disregarding this aspect makes modelled i.v. infusion into a restricted closed volume a more discriminating test. Equilibrium 5 is more rapid, and is probably what happens to most lipophilic water-insoluble drugs released from micelles in any case.

The main experimental difficulty in trying to model the infusion process with a medicinal product is that the drug would precipitate in dilute solutions below the c.m.c. of the surfactant.

The infusion process could be mimicked by infusion into a closed system representative of the blood compartment volume and temperature, of saline or preferably plasma. However, especially for plasma studies, the process may be scaled down, i.e. maintaining the same concentrations of the components but using smaller volumes.

Plasma-based studies would be more biologically relevant but the investigational methods are obviously more restricted, e.g. light-scattering techniques could be applied to drug-free systems in saline, but probably not in plasma. On the other hand, micelle properties may be investigated in plasma by using fluorescent-labelled surfactants, or a dye uptake method, e.g. a fluorescent probe like TNS [6-*p*-Toluidino-2-naphthalene Sulfonate] which fluoresces in the hydrocarbon interior of a micelle (or indeed any other probe), corrected for any dye that may be taken up by endogenous amphiphiles in the plasma. It may be possible to use the product itself, since there may be some residual cargo capacity remaining for the uptake of fluorescent dye.

10 Although it cannot be assumed that the c.m.c. in plasma is the same as the aqueous c.m.c.

11 Tellingen O, Beijnen J H, Verweij J, and others, Rapid Esterase-sensitive Breakdown of Polysorbate 80 and Its Impact on the Plasma Pharmacokinetics of Docetaxel and Metabolites in Mice , Clinical Cancer Research, Vol. 5, 2918-2924, October 1999 http://clincancerres.aacrjournals.org/cgi/content/full/5/10/2918

A recent *in vitro/in vivo* study of what happens to the micellar state after injection in animals has shown an apparent disintegration of micellar structure within 15 minutes, using Förster Resonance Energy Transfer (FRET) between a lipophilic donor/acceptor pair solubilised in a polymeric surfactant. In order for transfer of this resonance energy to be optimised, the donor and receptor couple must be confined in close proximity (typically ~10nm) as is the case in the restricted interior of a micelle. Loss of resonance energy transfer indicates a greater separation of the couple, as happens when the micelle structure is lost. This rapid loss of micelle integrity and release of core-loaded molecules was initiated by the presence of α- & β- globulins and interestingly occurred at concentrations of surfactant above the aqueous c.m.c.[12] FRET methods could indeed have some value in helping to understand what happens to the micellar system *in vivo*. Ideally, both lipophilic FRET probes, or fluorescent dye probes could be used with the product and a drug sink to indicate the presence or absence of a micellar system.

Furthermore, there is evidence that the biodistribution patterns of the radiolabels from ^{3}H-labelled paclitaxel solubilised in ^{14}C-labelled polymeric micelles are different, and that the patterns diverge rapidly after intravenous administration, paclitaxel showing a wide diffuse distribution different from the micelles. This indicates that they are not travelling together; the most likely explanation being that paclitaxel is rapidly released from the micelles after administration[13].

Nuclear (NMR) methods may also be useful to give information on the state of any exogenous micelles in the complex medium of plasma.

Finally it is important to highlight that the methods described above are non-standard techniques, which are not in common use because of the complexity of the biological environment and the difficulties associated with method validation.

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 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 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.

7. Generic Products and Post-Authorisation changes

This section relates to generics of those reference products containing active substances which are also solubilised in micellar systems; both products should meet the bullet points listed in the Scope of this paper. Concerning the Pharmaceutical Development of these generics, Sections 1 to 5 of this paper could be considered applicable in all cases.

Furthermore, very similar principles also apply to post-authorisation changes, e.g. variations. The basic questions are:

- What is the likely effect of formulation/manufacturing changes on biodistribution and/or pharmacokinetics?
- How can reassurance be provided in the form of in vitro studies?

12 Chen H and others, Langmuir, 24. 5213-5217 (2008)

13 Burt H M, and others, Colloids and Surfaces B : Biointerfaces 16, 161-171 (1999)

To avoid repetition, the following text refers only to generic medicinal products.

7.1. Bioequivalence Surrogate Markers

According to EU guidance on bioavailability and bioequivalence intravenous micellar injections can be regarded as 'complex' parenterals in which case a bioequivalence study may need to be performed regardless of the intravenous route. The basis for this classification is linked to the (theoretical) introduction of an additional micellar compartment or 'lipophilic phase' into the patient, i.e. the lipophilic interior of the micelle, compared to a 'simple' aqueous solution. The real extent and persistence of the micellar component *in vivo* may be called into question, since during the initial stages of a slow infusion the micelles may disappear because of dilution and thereafter by metabolism of the surfactant. Consequently the real effect of the surfactant on the bioavailability of the active substance may also be called into question.

The principles outlined below, although emphasised for generics, are equally applicable to any post-authorisation modification that might affect bioavailability.

If an applicant wishes to apply for an exemption from the need to perform a bioequivalence study - i.e. a 'biowaiver' - a complete biopharmaceutical argument should be proposed together with the results of relevant physicochemical tests as bioequivalence surrogate markers. In this regard, satisfactory development pharmaceutics, as described in sections 1 to 4 and some of the *in vitro* studies under sections 5 & 6 could be useful if performed in a comparative manner against the reference product.

Data requirements to support a biowaiver are briefly described in the guideline on the investigation of bioequivalence. Satisfactory development pharmaceutics data could support the submission of a reduced extent of clinical or non-clinical data, or its absence.

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 level of testing depends on how similar the generic is to the reference product in terms of qualitative and quantitative composition. However, since it is unlikely that the detailed composition of the reference product will be known, applicants will need to decide and justify the amount of information that is necessary to support any claim for a biowaiver. Applicants are strongly advised to seek scientific advice from the CHMP and/or National Competent Authorities.

7.1.1. Differences in the formulations

It would be unreasonable to require extensive testing of a generic micellar injectable product that is *identical* to the reference product. However formulation differences tend to be the norm rather than the exception.

In the case of generic products, applicants are advised to copy exactly the composition of the reference product as far as is known to them. Applicants should provide clear tables showing the concentrations of all ingredients, not only in their product as presented for the market, but also in the infusion solution(s) immediately prior to administration to the patient.

7.1.2. Identical Formulations

Same excipients, same amounts.

This is the simplest case, and minimum testing is required, utilising diluted solutions according to the SPC, immediately prior to administration. If the generic product is presented in a different pharmaceutical form compared to the reference, but the qualitative and quantitative composition of the diluted infusion is the same, such a product can be included in this section.

Comparative studies according to Section 5 could provide useful information in support of a biowaiver.

7.1.3. 'Similar' Formulations

The same surfactant is a condition.

Formulations may be qualitatively identical, with small quantitative changes only.

Alternatively, there may be qualitative differences in excipients, which are judged to be 'non-critical' in relation to their influence on micelle stability and bioavailability of the drug. In this regard the following should be noted:

- Small differences in the relative amounts of pH adjusting agents are not likely to have a significant impact on micellar stability or disposition of the drug in vivo, because of the great dilution in the plasma on administration. Ionic micelles are sensitive to the ions in their aqueous environment (ionic strength) but in general, the non-ionic surfactants most likely to be used in biological applications e.g. polysorbates or cremophors, may be less sensitive to changes in ionic strength;
- Small differences in the content of added co-solubulising substances such as PEG (same molecular weight in both products) or ethanol are not likely to have a significant impact on the micellar stability or disposition of the drug in vivo, because of the great dilution in the plasma on administration. The hydration corona plays a part in the stabilisation of non-ionic micelles and this can be reduced by alcohol and other polar solvents. However, low chain alkanols, such as ethanol only have this inhibitory effect when the concentration rises above ~ 10 % v/v. Concentrations in an infusion solution immediately prior to administration (and in vivo post-administration) are very much less than this.

As with identical formulations, comparative testing according to Section 5 could be useful in support of a biowaiver, but there is an increased risk that further information may be required if the non-critical nature of the qualitative/quantitative differences in the formulations proves difficult to determine conclusively.

The safety implications of differences in composition should always be discussed.

7.1.4. Different Formulations

Chemically different surfactant/micelle-forming system.

Alternatively, this may also apply to:

- The same surfactant, but used at a significantly different concentration compared to the reference product;
- Products in which there are qualitative/quantitative differences in other excipients which may have an impact on micelle stability and/or bioavailability of the drug.

The published transience and observed rapid loss of integrity of certain micelle systems *in vivo* supports the general view that relevant physicochemical testing to support a biowaiver for intravenous micellar systems should not be ruled *a priori* out of the question. However, if the generic product has a

different surfactant to the reference product, then it is unlikely that an *in vitro* comparison alone would be sufficient to support a biowaiver. With different surfactant systems there is a risk that at least a bioequivalence study would be needed, with the possibility of additional nonclinical and/or clinical studies. These are clinical decisions, taking into account the following issues, and others:

- The metabolism of the surfactants may be different, and this may have an effect on the extent and persistence of the micellar compartment in vivo;
- There may be differential drug binding to surfactant monomer and consequent effects on drug clearance;
- The different safety profiles of the surfactants per se needs to be considered, together with the possibility of different interactions with co-administered drugs;
- Surfactants may affect transporters and enzyme systems thus modifying drug disposition.

These investigations are not strictly part of Pharmaceutical Development in Module 3, although a summary could be made referring back to Module 3 in order to support the findings of any physico-chemical studies.

If biomimetic models are used, such as those described in Section 6, applicants are strongly advised to discuss their development with the competent authorities and/or to seek scientific advice from the CHMP or National Competent Authorities, in order to reach an agreement not only on the level of testing which is required, but also what is feasible.

If no convincing evidence can be obtained from *in vitro* studies, applicants should provide relevant *in vivo* efficacy and safety studies. With respect to efficacy, this may be addressed by appropriate pharmacokinetic studies showing equivalent disposition.