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Committee for medicinal products for human use (CHMP)

Overview of comments received on Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product. (EMA/CHMP/SWP/620008/2012)

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

Stakeholder no.	Name of organisation or individual
1	David Snodin, Xiphora Biopharma Consulting
2	Iron4u, Dronninggårds Allé 135, DK-2840 Holte
3	IFAPP (International Federation of Associations of Pharmaceutical Physicians)
4	Members of the Ph.Eur. NBC (Non-biological complexes) Working Party
5	Azad Pharma AG, Toffen, Switzerland
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Bias by omission of key facts Abuse of scientific method Absence of data supporting recommendations Lack of validation of proposed test methods Unnecessary use of animal studies Publication of external comments and EMA responses Avoidance of citing confidential data that cannot be subjected to any third-party evaluation Reflection paper should be withdrawn Maintenance of transparency Use of public domain data.	Not accepted. General comments do not reflect the aim of the RP.
2	Intravenous iron formulations, are very different from both small molecules and biologicals used as medicinal products. Iron is a nutrient fundamental to all humans. When intravenous iron medicinal products are used, an accurate diagnosis is required and the dosage is adjusted to normalize body iron stores. Thus, provided iron can be delivered safely to the primary target organ, the RES, the risk of toxic effects due to over-dosage should not exist. However, iron cannot be delivered safely to the RES by intravenous administration of simple iron salts, as free iron in plasma is highly toxic. Therefore, intravenous iron has to be shielded which can be achieved by various carbohydrates; this has led to the development of the iron-based nano-colloidal products. Iron is the biological active substance in all iron containing intravenous medicinal products. The products all consists of an iron core shielded by glucan in order to circumvent the immediate toxicity of dosing simple iron salts intravenously. Iron isomaltoside 1000 is the only known exception, as it is structured in a matrix of interchanging iron and carbohydrate molecules. The various glucans used as a shield of the biological active iron influences the size of the iron core and the size and	Not accepted. Comparison with a reference product having a different glucan in the coating is not revealing the information whether reference and generic product are similar.

	stability of the iron glucan complex (i.e., the release of labile iron in plasma). The active part of the molecule is the iron core and this is "similar" in almost all formulations (except of Monofer). The surrounding sugar could be considered just as a "carrier" and all of them are "glucose-based" oligosaccharides or polysaccharides. The differences are in the number of glucose units and the types of glucose bonds, that could be considered as "difference in the manufacture process", which in turn results in differences in properties of the final product The stability of the iron glucan complex determines the toxicity, consequently low stability complexes are subject to smaller doses in order to avoid acute iron toxicity. Further, the glucan may have impact on the antigenicity of the product, as has been suspected especially for the iron products relying on dextran as the glucan. Three assessments reports on intravenous iron containing drugs can be found in the public domain: Monofer 100 mg/ml solution for injection/infusion (iron(III) isomaltoside 1000), SE/H734/01/DC. Monofer was approved based on reference to literature and reference to iron dextran medicinal products with dextran of higher molecular weight, supplemented by a short-term piglet study and 2 human studies on total 202 patients receiving a 8 week treatment course. Ferinject 50 mg/ml Solution for Injection/Infusion (ferric carboxymaltose), UK/H/0894/01/E01/MR. Ferinject was approved based on extensive both non-clinical and clinical data, and the safety database included 899 patients. Rienso (Ferumoxytol), EMEA/H/C/002215. Rienso was approved based on extensive both non-clinical and clinical data, and the safety database included 1726 patients. A review of the above assessment reports demonstrates that 1) if given at very high doses to animals, iron is toxic: and 2) if delivered intravenously to humans, iron will be available for erythropoiesis. Whether more subtle advantages or disadvantages are caused by either temporary labile iron or the ability to deliver iron for erythropoiesis was not revealed. It seems obvious, that a drug development program on a new iron glucan based on classical	

	paradigms for drug development will demonstrate the obvious. If given in excessive doses iron is toxic, and both oxidative stress and hemosiderosis will develop. The present ”Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal products” proposes to use more specific methods to determine the risk benefit of a new intravenous medicinal iron containing drug developed with reference to an innovator medicinal product. The proposed methodology applied to the above-referred new drugs would also have provided additional valuable knowledge to the efficacy/safety profile of the drugs assessed. Oxidative stress models have been able to discriminate between iron containing drugs based on identical glucans (Toblli et al, 2009). In addition, more detailed information on biodistribution could give a better estimate on both the potential toxicity and the delivery of iron to target tissue. None of the above-mentioned assessment reports presented data on the evaluations of oxidative stress in animals, which would have been superior to conventional methods in revealing the potential of these formulations to cause iron toxicity. The stability of the various iron glucan complexes in plasma was not documented, thus the risk for releasing free iron, though at low concentrations, still exists. We propose that the paradigms presented in the ”Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal products” to be used also for the evaluation of iron nano-colloidal products which contains a different glucan. This is in order to provide better risk benefit assessment and to avoid uninformative animal and human experiments. The Fe(III) should be regarded as the active ingredient which is carried in a carbohydrate shell. The carbohydrates in the reference intravenous iron complexes should be regarded as different ligands of the same active ingredient. Therefore, it appears appropriate to ensure that any glucan, when used as a substitute for another glucan, is safe by demonstrating that: The glucan is a strong chelator to shield the iron into a stable iron complex The glucan does not negatively influence the in vivo efficacy of the intravenous iron complex	

	The glucan does not negatively contribute to the safety of the intravenous iron complex.	
3	We agree on the overall contents of this guideline, but we suggest that more emphasis is placed on RMP	Partially accepted. New wording of RMP section was included in RP.
4	1. The terms "coating materials" and "carbohydrates" are used throughout the document with the same meaning. In order to avoid confusion only one should be used. It would be preferable to use “carbohydrates”. Furthermore, “coating” might not be the correct term. E.g. line 120 should read carbohydrate instead of coating material. 2. In terms of patient safety it is considered useful to add an acute toxicity test. 3. Literature references would be useful.	Accepted. ‘coating materials’ has been replaced by ‘carbohydrates’. Not accepted. An acute toxicity test would not add more information due to relative insensitivity compared to the biodistribution study. Partly accepted. Peer reviewed publications of preclinical biodistribution studies specificly for this kind of medicinal iron products are scarce. As examples could be mentioned: Elford P et al.: Biodistribution and predictive hepatic gene expression of intravenous iron sucrose. J Pharmacol Toxicol Methods 2013; 68: 374-383. Praschberger M et al.: Bioavailability and stability of intravenous iron sucrose originator versus generic

		sucrose AZAD. Pharm Dev. Technol 2013 Nov. 13. Roth S et al.: Comparative toxicity and cell-tissue distribution study on nanoparticular iron complexes using avian embryos and HepG2-cells. Transl Res 2008 Jan;151(1):36-44. Toblli JE et al: Comparison of oxidative stress and inflammation induced by different intravenous iron sucrose similar preparations in a rat model. Inflamm Allergy Drug Targets 2012 Feb;11(1):66-78. Toblli JE et al.: Comparison of the renal, cardiovascular and hepatic toxicity data of original intravenous iron compounds. Nephrol Dial Transplant 2010 Aug 19. Though it would be good scientific practice to have a literature list added, in this special case it is difficult to find publications of authors who are not in parallel involved in the marketing of this kind of iron products. Therefore, we prefer not to

		include such a list in the RP.
5	1. Introduction The tests for physicochemical analysis available today are many and precise so we do feel that a statement (line 56) such as “the inability to fully characterise and define coated iron based particles using quality methods alone” is misleading, given that such tests are validated and yield detailed quantitative data. The “further investigations” being proposed would necessitate using qualitative tests - as discussed in section 2.1.1 of the draft and about which we will comment later - the relevance of which both in terms of a suitable specification and how values obtained may impact on the fate of such products in vivo is at present speculative. Surely the Reflection Paper (RP) should focus upon how to show essential similarity between the reference and the generic using the validated tests and compedial specifications and not attempt to demonstrate this based on approaches and tests whose current place is more suited to the research laboratory. ICH and EU Guidelines We fully understand that originators will try to defend their products and market in the face of generic competition. However, with regard to iron sucrose generics, the originator - through various sponsored publications and round-table forums - has coined the term “iron sucrose similars”, or “ISS”, on the one hand to question the equivalence (quality and safety) of the generic products and on the other, having the aim of establishing a mind-set that iron-based products should be encompassed within the scope of biosimilars, with the extensive development requirements and costs that this entails. In this respect, it is noticeable that several guidelines relating to biological/biotechnological products have been cited in the draft RP as being relevant to iron-based products. It has to be pointed out (as summarised in the table below) that these products are very different to biologicals (and biosimilars) and therefore, in our opinion, it may not be appropriate to reference biologics guidelines in this RP?	Usefulness of human PK is supported, clinical efficacy and safety study are addressed below.

SMOLs (small chemically manufactured molecules)	**Biologics (Biopharmaceuticals)**	**Polynuclear Iron-formulations (example, iron sucrose)**
Small, completely defined molecule	Large (up to 150kDa) and sometimes not completely defined proteins	Medium-sized (up to 60 kDa) with defined chemical components
Chemically synthesized	Produced by biotechnological	Chemically synthesized

	processes	
Highly defined specification	Specification using values within certain ranges	Specification has both highly defined and value ranges
Known impurities with unknowns kept within defined low values	Possible impurities (e.g. due to post translational modifications) not well definable	Known impurities with unknowns kept within defined low values
Analytics: chemical and physical tests	Analytics: necessitates complex measurement of biological activity (bio-, immunoassays)	Analytics: chemical and physical tests
Computation of solvent structure and related properties	Computation of crystal/NMR-structure	neither
molecular weight precisely determinable	Molecular weight with variation around 1 Da	Molecular weight with variation 1000 Da
Metabolism known at molecular level	Metabolism known at molecular level in many cases	Metabolism at molecular level unknown
size precisely known	Size known for globular proteins	Large variation of particle size

2.1 Quality

We agree with the statement that an extensive comparability exercise is required to demonstrate that the iron-based colloidal product has a highly similar quality profile when compared to the reference medicinal product. The reference product has of course been subject to such detailed physicochemical analysis and any generic product must be subject to the same stringent evaluation. Given that most of the compedial specifications are ranges, we agree that such an analysis must involve more than single batches of both the reference and the generic in order that a proper evaluation can be made (both inter- and intra-product). A proposed set of analyses is given in the draft under 2.1.1 Quality characterisation of the test product. Here it states that “A list of tests to be applied routinely to the iron-based product should be defined, taking relevant pharmacopoeial monographs into account”. BP and USP Monographs define iron sucrose specifications and these have been in place for a considerable time and until now have been deemed sufficient. Although the list of relevant physicochemical parameters given in 2.1.1 is, in our opinion, reasonable, we do not understand the logic of attempting to include qualitative tests of unproven relevance as release

	specifications. With reference to the kinetic studies of iron (III) reduction, it should be noted that the originator patented the test referred to in the draft RP, an action which would have considerably hindered the development of generic products, but it was revoked by the European Patent Office following a legal challenge. In the European Patent's Office's decision it was concluded that to link the test (and a test specification such as "T75 < 20 minutes") with an activity profile (of bioequivalence) following administration to a subject is not technically meaningful. It is now proposed to add this test as a release specification, although no detailed analytical (validatable) method is available nor are any acceptance limits given - only "to release acceptable amounts of iron". Who is to determine what, in this not fully-defined biological system - actually is an acceptable amount that could, based on good scientific rationale, be used for batch release? For example, although the originator uses an in-house specification for degradation of 7.5 – 14.0 minutes (Arzneimittelforschung 2009; 59:176-190), a subsequent US patent application (US 2010/0248376 A1) by a different company suggests that a T75 of 25 – 50 minutes "indicates bioequivalent iron-sucrose composition". The suggestion that an in vitro labile iron donation test should also be used as a release test begs the questions (1) how can such an assay be validated and (2) again, what should be taken as an acceptable level of labile iron release. The suggestion that limits "should be set based on batches previously demonstrated to be safe with regard to labile iron in in vivo studies" may well prevent development of all generic iron-containing medicines since to undertake such extensive in vivo testing of a number of batches would probably be financially prohibitive for generic companies. To add the above iron release and labile iron tests as release specification raises an unreasonable barrier, given that these tests were not required for the marketing approval of any current intravenous iron-containing reference product and have not been used as release specifications during the decades in which these products have been used. Such analyses can be part of the development report of a generic product, but once physicochemical and such functional similarity has been shown at that stage, such qualitative tests have no practical place for routine release testing in a manufacturing facility's quality control laboratory. The section 2.1.2 "Establishing pharmaceutical comparability between test and reference product" is an extension of the previous section and makes reasonable sense in our view.	

	2.2 Non-clinical This section focuses on bio-distribution studies and is effectively a copy-paste of the RP published in March 2011, which at that time the EMA stated was required “to support the claim of essential similarity of generic and reference NPI medicinal products”. We have no comments on this section, since we have already completed the work that was requested in that RP (see below). 2.3 Clinical The suggestion for pharmacokinetic studies is a surprising requirement, given that the position cited in the RP of 2011 that a bioequivalence study is of limited value given the pharmacology of iron-containing medicines: “a pharmacokinetic comparison of different products based on the measurement of plasma concentrations may only reflect the clearance from plasma but may well fail to detect in which extent the nanoparticles are taken up by different target organs”. Following a Scientific Advisory Meeting with MHRA we were recommended and successfully followed the RP 2011 approach (studies published in J Pharmacol Toxicol Methods 2013; 68: 374-383 & Pharm Dev Technol 2013 Nov 13. [Epub ahead of print, DOI: 10.3109/10837450.2013.852575]. The reason for such a change of thinking by CHMP is unclear to us, but may well be due to influence from the FDA Draft Guidance on Iron Sucrose (Recommended March 2012; Revised November 2013) which does require demonstration of bioequivalence in a standard pharmacokinetic study? Recently the EMA published “New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines” (EMA/377372/2013) as a conclusion of the Article 31 of Directive 2001/83/EC, initiated by the ANSM due to concerns over the risk of serious allergic reactions. This referral procedure examined the safety profiles of all iron containing medicines (reference and generic) having marketing authorisations and having been commercialised within the EU. It was concluded that the risk benefit of intravenous iron containing medicines is favourable but that the risk of hypersensitivity necessitates new recommendations to health care professionals and patients (as published in EMA/377372/2013) and that MA holders should monitor the incidence of hypersensitivity reactions through a post-marketing epidemiological studies. The referral procedure found no evidence of any general safety concerns related to generic versus reference products and indeed, the originator and generic companies were recommended to pool resources and data to develop a risk management plan for the post-marketing pharmacovigilance studies.	

	We therefore question what EMA has in mind regarding section 2.3.2 “Efficacy and safety studies”, since here it states that “Provided that the totality of data i.e. quality comparison, non-clinical data and the human PK study demonstrate similarity, a further therapeutic equivalence study to demonstrate comparable efficacy and safety is generally not necessary”. Surely, if all aspects of the data demonstrate similarity what is the need to ask for a safety and efficacy study? To the leave door open for an authority to perhaps demand such a study after all other data has shown similarity, may well deter generic companies from the large investment required to gather the data in the first place. The EMA has already changed its opinion on data requirements with this new draft RP compared to that of 2011 and therefore companies such as ours with limited resources would be very wary of risking development of their generic iron-based product with this extra highly expensive demand for an efficacy and safety study – when all other data shows similarity – being present. We would strongly suggest that this wording be amended to state simply that if the data shows similarity the product is approvable. Summary We have recently learnt that the EDQM has initiated a NBC working party with the aim of formulating a European Monograph for Iron Sucrose Concentrated Solution and that the quality parameters being considered are a mirror image of those in the draft RP. Therefore, our comments to the Quality aspects of this draft RP are also relevant to the setting of a Monograph specification: much of the quality considerations of the draft do make good sense, but the proposed functional tests should be part of the development and characterization of a generic product (in comparison to the reference product), not part of routine release testing. Likewise, the citing in the draft RP of guidelines on biotechnology products is, in our opinion, inappropriate. In the table below we have listed those quality aspects that should in our view be retained and those which should be excluded. This, together with the recommendations of the Article 31 referral mentioned above, could in our view constitute a final and defining template for the development and characterisation - and for the safe clinical use - of iron containing medicinal products.	

Proposal of acceptable / non-acceptable parameters for adequate quality characterization and pharmaceutical comparability

Parameter	Include / Exclude	Comments
Quality standard for coating materials of both API & FP	Include	In development report
Structure and composition of carbohydrate	Include	In development report
Key intermediates	Include	In DMF (?)
Particle size & surface area of iron core	Include	In development report
Fraction of labile iron released when administered	Exclude	How can this be feasibly tested in development of generic? Take from the literature and add to development report.
Polymorphic form of iron	Exclude	Relevance unknown
Impurities	Include	DMF & release specification
Morphology	Include	In development report
Ratio of carbohydrate to iron	Include	In development report
Particle size, distribution etc	Include	In development report
In vitro iron release rate (labile iron / acid degradation)	Include	In development report, not as release specifications
Degradation path for carbohydrate / iron complex	Exclude ?	Take from the literature?
Stability on storage	Include	In development report
In-use stability	Include	In development report
Comparative stress test studies	Include	In development report

6	A. Introduction and general comment We welcome the document reflecting the current thinking of the CHMP for the regulatory submission and data requirements for the comparability of nanoparticle, non-biological complex products. We provide our comments on the document according to the given structure of the Reflection Paper (RP). We include our expertise and knowledge as the manufacturer of the originator medicinal product (MP) iron sucrose (Venofer®) authorized since almost 65 years in Switzerland and currently registered in more than 90 countries world-wide. We provide our comments based on our extensive	Usefulness of human PK is supported, clinical efficacy and safety study are addressed below.

experience which led to the discovery and development of a variety of different currently marketed iron-based nano-colloidal MPs. In particular, we have gathered a deep knowledge on the properties of the iron sucrose originator and carried out a series of experimental investigations on iron sucrose similars (ISS).

To show comparability of an iron-based nano-colloidal MP developed with reference to an innovator MP, a stepwise approach as indicated below makes sense for the overall assessment of the required data. The polymeric nano-colloidal MP is characterized by a polynuclear iron(III)-oxyhydroxide core stabilized by mono-, di-, oligo- or polysaccharides. It consists of a mixture of similar, non-homomolecular macromolecules as defined for non-biological complex drugs (NBCDs) [Crommelin et al. AAPSJ 2014;16:11-14]. In contrast to well defined low molecular MPs, these compounds cannot be fully characterized by physico-chemical means. Therefore, additional non-clinical and clinical data are needed to adequately assess such a MP and to conclude there is sufficient similarity between a test and reference product and, eventually, there exists therapeutic equivalence [Schellenkens et al. Reg Tox Pharmacol 2011;59:176-183. Schellekens et al. AAPSJ 2014;16:15-21].

The stepwise evaluation of the required data goes through three levels:

1. A physico-chemical product characterization.

2. A non-clinical assessment focusing on toxicology as well as biodistribution studies.

3. A clinical assessment in normal volunteers and in an appropriate patient population for comparability based on both a bioequivalence and therapeutic equivalence (TE) approach, which for these iron-based nano-colloidal MPs requires a pharmacokinetics study as well as a safety/efficacy Phase III trial.

The 1st level has to be based on validated and state-of-the-art analytical methods with the necessary sensitivity and robustness to demonstrate similarity between the reference and test MP to continue on to the next level. As discussed in more detail below, this is not always the case for the proposed methods. Moreover, it is currently not known how and what differences in physico-chemical parameters impact the clinical safety and efficacy of the MP and thus a broad spectrum of

different parameters needs to be included.

The data on the 2nd level have to demonstrate similar tissue targeting as well as biodistribution in the correct cellular compartments between the products in a standardized animal model. We believe that this non-clinical evaluation is mandatory to obtain the necessary insight into the comparability of the fate of such a nano-colloidal MP but, again, the challenge is to develop a well-defined biological model suitable for this assessment. Non-clinical assessment should also compare the potential of these MPs to induce oxidative stress and inflammation, properties that may be important for safety issues or indicative of different targeting and biodistribution (see below sector C). Only upon demonstrating non-clinical similarity between the products can the next level of clinical comparability be assessed.

The 3rd level data requirements include classic bioequivalence studies with an intravenous (I.V.) formulation, which are normally governed by the clearance of the MP from the plasma (concentration over time). However, plasma concentrations of the MP are not indicative of biodistribution of such nanomedicines and in particular for I.V. iron products that interact with the highly controlled physiological iron handling processes (see sector D). Clinical evaluation requires not only a pharmacokinetics (PK) study but also a study that demonstrates the effective delivery of iron from the MP (pre-drug) to its site of action, e.g. the hemoglobin. Only a sufficiently powered head-to-head clinical investigation in an appropriate patient population will provide the necessary data to fully evaluate the properties and characteristics of the products necessary to determine TE, the prerequisite for substitutability and interchangeability between products.

Only the totality of the data on all three levels allows full characterization of the products to assess comparability and eventually TE of a newly developed MP with reference to the originator MP.

B. <u>The physico-chemical testing</u>

I.V. iron-based nano-colloidal MPs consist of a polynuclear iron(III)-oxyhydroxide core stabilized by a carbohydrate shell. Whereas the composition of the iron cores is rather similar, a wide variety of carbohydrates have been employed for the shell, among others, monosaccharide derivatives (gluconate), disaccharides (sucrose), oligosaccharides (reduced Dextran 1), and polysaccharides (carboxypolymaltose, dextran-derivatives). Because of the polymeric nature of the carbohydrate ligand and/or the iron core, these compounds are not well-defined molecules but are instead made

	of a mixture of similar (closely related) molecules with a range of molecular weights within the specified molecular weight distribution. The exact composition of this mixture is largely defined by the manufacturing process. Small differences in the starting materials or reaction conditions (e.g. pH, temperature, reaction times) may have a significant impact on the physico-chemical properties of the final product. Thus, as suggested in the RP, a series of comparative physico-chemical analyses of the test and reference MP are required to determine the extent of “similarity” (or “sameness”) of such NBCDs, also called nanosimilars [Ehsam et al. Nanomedicine 2013; 8:849-56]. However, the challenges are to identify clinically meaningful quality attributes with an impact on disposition, safety and efficacy of the MP as well as to define the required extent of similarity (e.g. by statistical comparison of results) [RP on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/08/WC500147874.pdf]. There are currently no data that allow for a reliable correlation between the list of attributes given in the current version of the RP (starting on page 4) and the efficacy and safety of these MPs. For instance, it is clear that the fraction of labile iron in the I.V. iron-based nano-colloidal products may have an impact on the safety, and possibly efficacy, of the product. However, there are no data that definitively associate this quality attribute to a clinical outcome. One of the reasons for the lack of correlation is that the amount of labile iron measured in these I.V. iron products strongly depends on the analytical method used to quantify it [Van Wyck. Nephrol Dial Transplant 2004;19:561-565. Jahn et al. Electrophoresis 2007; 28: 2424-2429. Balakrishnan et al. Eur J Clin Invest 2009;39:489-96. Stefansson et al. Nephron Clin Pract 2011; 118:c249-c256. Jahn et al. Eur J Pharm Biopharm 2011;78:480-491]. The two methods mentioned on page 6 may be useful to compare the reference and the test compounds, but will not provide information on the clinical impact of identified differences. Specifically, “kinetic studies of iron(III) reduction by acid degradation and I.V. measurement” are performed in vitro under conditions significantly different from the physiological conditions within the human body. Thus, it will be impossible to assess the impact of any differences in the absolute values obtained with this test on the safety and efficacy in the clinical setting.	

	The second point mentions that “limits for direct in vitro labile iron donation should be set based on batches previously demonstrated to be safe with regard to labile iron in in vivo studies”. However, this requirement implies the availability of clinical data with various preparations, which would allow for the determination of this specification. These data are currently not available for the marketed I.V. iron-based nano-colloidal products. Moreover, as mentioned above, the absolute amount of labile iron strongly depends on the analytical method used to quantify it. Importantly, non-clinical studies have shown that the labile iron is not directly related to or the only cause of oxidative stress caused by I.V. iron preparations. The nature of the complex and/or the core also plays an important role [Bailie et al. Biometals 2013;26:473–478. Koskenkorva-Frank et al. Free Rad Biol Med 2013;65:1174–1194] and other unknown differences may be relevant. Further issues are that the majority of the parameters that are mentioned as important for characterization of the test products are not well defined and many of the analytical methods available to determine the requested physico-chemical parameters have not been validated. Therefore, very little guidance is provided as to how sameness can be established between the test and reference MP. The difficulties in determining some of these parameters are highlighted by the fact that there are disagreements in the scientific literature with respect to the particle size of iron sucrose. While Kudasheva et al. [J Inorg Biochem 2004; 98:1757-69] report a particle size of 22 nm, others have suggested that the particle size is 8 nm [Jahn et al. Eur J Pharm Biopharm 2011;78:480-491]. As the determination of the particle size depends on the method applied, a standardized method for sample preparation and determination of the particle size have to be established. An additional parameter on the list in the RP is the polymorphic form of the polynuclear iron core which is an important parameter for the characterization of the polynuclear iron core. However, this measurement can also be challenging depending on the size and degree of crystallinity of the compounds. For instance, data in the literature show that certain tests such as X-ray Diffraction (XRD) yield conflicting and, thus, inaccurate results. Indeed, the core structure of iron sucrose was assigned as a ferrihydrite, a ferrihydrite with possibly other structures mixed in such as akaganeite, as a lipidocrocite or ferrhydrite, or as akaganeite [Funk et al. Hyperfine Interactions 2001;136:73-95. Jahn et al. Eur J Pharm Biopharm 2011;78:480-491. Kudasheva et al. J Inorg Biochem 2004;	

98:1757-69. Futterer et al. J Pharm Biomed Anal 2013;86C:151-160].

The RP also includes particle morphology in the list of attributes to be determined, suggesting microscopic evaluation of iron distribution in the iron complex. Two techniques [i.e. atomic-force microscopy (AFM) and transmission electron microscopy (TEM)] can conceivably be applied. Vifor's experience with AFM, however, suggests that the results of this analysis strongly depend on the sample preparation. AFM is also qualitative in nature and is therefore difficult to standardize and validate [Kudasheva et al. J Inorg Biochem 2004; 98:1757-69]. TEM may be better suited to determine particle morphology, but it does not offer any advantage in terms of standardization and validation of the method, and thus in terms of demonstrating "sameness". Neither method provides valuable parameters that would allow for discrimination between the MPs or demonstration of similarity.

In conclusion, because of the difficulties linked to these techniques, we would strongly recommend that EMA require that an applicant provides the necessary background and rational to convincingly demonstrate that the applied methods and data are robust, sensitive and indicative for the purpose of showing comparability and are capable of excluding any differences that are important for the characterization of the MPs.

For some of the I.V. iron-based nano-colloidal products Pharmacopoeial monographs are available or under elaboration. These should provide the starting point for the physico-chemical characterization of these MPs and the inclusion of the detailed list of tests from these monographs would be very useful. Nevertheless, it should be emphasized that various non-clinical studies by Toblli et al showed that, compared to the iron sucrose originator, increased oxidative stress levels were induced by iron sucrose similar products including a product that met the United States Pharmacopeia physico-chemical reference values for iron sucrose injection [Toblli et al. Drug Res 2009;59:176-90. Toblli et al. 2012. Inflamm Allergy Drug Targets 2012;11:66-78]. Thus, these study results demonstrate that similar physico-chemical properties do not ensure similar toxicological effects and thus, as suggested in the RP non-clinical (toxicology) as well as clinical studies are necessary and required.

Finally, it is important to keep in mind that the iron sucrose complexes which are formulated at a pH 11 will be quickly modified when injected into the bloodstream (blood pH 7.4), possibly changing

the size and surface properties of the complexes. The size and surface properties are not only important for the uptake (by the macrophages of the reticuloendothelial system) and distribution processes but also for the extent of direct release of iron from the injected complex, all of which have the potential to impact both the safety and efficacy of the MPs.

C. Pre-clinical data

The animal data are necessary to obtain information on the biodistribution of nano-colloidal I.V. iron carbohydrate complexes. In addition, the fate of the MP also needs to be assessed on a cellular level as mentioned in the RP, e.g. in the liver Kupffer cells or hepatocytes [RP page 8, line 265]. The challenge is to develop an appropriate and robust animal model with in-depth characterization of the species and defined sensitivity and repeatability. Based on the considerable amount of pre-clinical studies carried out with the iron sucrose originator and ISSs, it is apparent that these models are difficult to standardize, as confirmed by the Toblli et al. and Meier et al. publications [Toblli et al. Drug Res 2009;59:176-90. Toblli et al. 2012. Inflamm Allergy Drug Targets 2012;11:66-78. Meier et al. Drug Res 2011;61:112-119].

We agree on the proposed approaches requiring analysis of defined compartments (tab. 1 of RP) as initially addressed in the 2011 EMA RP [Non clinical studies for generic nanoparticle iron MP applications]. However, it is also important to compare the potential of the MP to induce oxidative stress and inflammation [Toblli et al. Inflamm Allergy Drug Targets 2012;11:66-78. Martin-Malo et al. NDT 2012;27:2465-71]. Such effects might be triggered by differences in biodistribution giving a hint of potentially significant and meaningful clinical differences of a MP.

The use of (non-invasive) imaging techniques like MRI might be acceptable if shown to be meaningful for the MP of interest. The methods have to be validated as they are not yet state-of-the-art in the non-clinical setting. In addition, the specific “paramagnetic” properties of the MP are key and must be specified in order to obtain the necessary sensitivity that is required to define a time-dependent distribution of the MP including potentially the degradation profile. Therefore, there is a need for basic validation studies to define sensitivity, variability, and limits of such methods.

Importantly, the mentioned non-clinical studies can potentially identify meaningful differences but on their own are not sufficient to prove similarity of the MPs. Therefore, we consider a clinical assessment in a sensitive patient population compulsory for evaluation of comparability based on

both a bioequivalence and therapeutic equivalence (TE) approach. For these iron-based nano-colloidal MPs, this implies that both a PK as well as a safety/efficacy Phase III clinical trial must be performed.

D. Clinical data

Human data requirements include a dual evaluation, namely a PK "bioequivalence" assessment and an additional safety and efficacy evaluation. This approach is acknowledged and supported. But in contrast to the proposal where it is stated, "that it is generally not necessary to conduct a TE study to demonstrate comparable efficacy and safety," we stress the need for the compulsory use of such clinical studies. This recommendation is based on published evidence of the differences between the iron sucrose originator and ISSs (both clinical and non-clinical) and the known influence of disease state on iron disposition and the resultant consequences for TE. In addition, it is not clear on what basis acceptable or minor variations or differences in human PK tests can be assessed for their impact on safety and efficacy comparability. Therefore, based on our current knowledge and experience, we do not know of any adequate substitution for a randomized, controlled safety and efficacy study to demonstrate TE and to eliminate any safety concerns.

A classical bioequivalence assessment for such products is difficult and not possible due to the nano-colloidal properties [Desai AAPSJ 2012;14;282-95; Cook J Bioequiv Availab 2011; S1 http://www.omicsonline.org/0975-0851/JBB-S1-003.digital/JBB-S1-003.html] and the lack of knowledge of a relevant central compartment controlling the overall PK and ultimately the efficacy and safety of these products. In addition, iron is a highly controlled essential element within the body with multiple modulating factors affecting its uptake, distribution, storage, incorporation into hemoglobin and other bodily processes, and re-utilization from physiological breakdown products [Andrews. Blood 2008;112:219-230]. All of these factors complicate the assessment of "bioavailability" of such complex pre-drug MPs. In addition, the fate of the I.V. administered iron complex is significantly influenced by the underlying disease and the body's need for iron. Therefore, iron bioavailability should be assessed using a quantifiable measure of the proportion of total iron that is absorbed, metabolized and utilized, i.e. that is incorporated into hemoglobin.

A PK study in healthy volunteers similar to that conducted by Danielson et al. [Drug Research. 1996;46(I):615-619] for Venofer® using a Michaelis-Menten compartmental model may be a

	reasonable study design as a starting point for assessing the PK characteristics of MPs (e.g. an ISS compared to the iron sucrose originator) but should not replace an appropriate TE study in patients. This is because it is unclear what impact differences in traditional PK parameters in healthy individuals will have on the comparability of the safety and efficacy of nano-colloidal MPs in patients. It is also important to acknowledge that the amount of iron in the serum represents only a small portion of the iron that is transferred to the site of action, and this amount is not proportional to the peak serum iron concentration or the AUC but to the rates of iron transfer to and elimination from the serum. Transferrin saturation is often used in clinical practice, however, it is known to be influenced by diurnal variation as well as the dynamic processes of iron metabolism and utilization which is modified by the patient's underlying disease state, iron status, use of erythropoiesis-stimulating agents, and hemoglobin level. In addition, the measurement of transferrin saturation is influenced by the iron dosing regimen and the timing of measurement in relation to the iron dose given. Therefore, the use of this measurement to assess comparability of MPs is wrought with variability and hence difficult to interpret. In addition, due to the not fully understood, non-linear kinetics of the ADME processes of nanomedicines, a potential dose dependence of PK is given and should therefore be taken into consideration. The PK aspect is also addressed by FDA in a guidance for a non-classical bioequivalence assessment in humans for such MPs [FDA guidance for different I.V. iron carbohydrate MPs, e.g. for IS http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM297630.pdf]. Although the guidance does not address efficacy and safety, such assessments need to be evaluated according to regulatory requirements (see also the Nulecit® case below). Evidence of clinically relevant efficacy and safety differences between nano-colloidal I.V. iron sucrose products has been shown by several investigators in various patient populations after patients were switched from iron sucrose originator to an ISS. [Rottembourg et al. Nephrol Dial Transplant. 2011;26:3262–3267. Stein et al. Current Medical Research & Opinion. 2012;28:241–243. Lee. Current Medical Research & Opinion. 2013;29:1–7.]. In addition, another clinical study by Martin-Malo et al (Nephrol Dial Transplant. 2012;27:2465-71) also clearly demonstrated that significant differences exist in oxidative stress, cell activation. and apoptosis between iron sucrose originator and an ISS. Based on the above clinical evidence and the lack of knowledge and	

	understanding of how differences in physico-chemical properties (resulting from different manufacturing processes) and non-clinical data may impact clinical outcomes in patients who use these products, it is necessary to conduct adequately powered human studies to demonstrate TE with certainty. As an actual example, FDA has recently scheduled a re-evaluation of an authorized iron gluconate follow-on product compared to the innovator product to assess the validity of their authorization data requirements and tools [Nulecit® scrutiny 2013 https://www.fbo.gov/index?s=opportunity&mode=form&id=592788989854da145c8e7b6d103c898d&tab= core&tabmode=list&]. A clinical trial for comparison is recommended, most probably using different dosing regimens (amount and timing), to show therapeutic and safety equivalence in relevant patient groups. These data will provide essential characteristics needed to profile and compare MPs as also discussed in the respective EDQM working party (non-biological complexes) for Pharmacopoeial monographs. In addition these data are a prerequisite for the substitution or interchange of such nanosimilars to be decided by the national authorities. In conclusion, with biosimilars there is a general reluctance to interchange or substitute a not fully identical complex MP with an alternative similar product. This should also apply to nano-colloidals or nanosimilars.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
36	4	Comment: This is also based on clinical experience. Proposed change (if any): current scientific knowledge and clinical and regulatory experience (…) indicate	Not accepted. "Current scientific knowledge" includes clinical knowledge.
38	5	Comment: Disagree that quality characterisation would necessarily be insufficient, in our opinion it could be sufficient Proposed change: Change “would” to “may”	Not accepted. The whole RP was initiated due to the view that quality assessment on its own cannot assure similarity in any case of nano-sized colloidal iron preparations.
38, 65, 83, 92, 185, 209, 283, 286, 304	2	Comment: Similarity in principle indicates not significant superiority or inferiority with respect to comparator. The term similarity excludes the possibility to approve a comparable product that is superior to the reference product (e.g. more stable, less free/labile iron). It would be more appropriate to use the term non-inferior, which would open the possibility for products based on a different carbohydrate to be also covered by the guideline. Proposed change (if any): Similarity -> non-inferiority or comparability	Not accepted. Aim of the paper is to discuss iron nano-preparation with the same carbohydrate coating in the test and the reference product. Therefore, the central issue is similarity and not inferiority or non-inferiority of the new product compared to the reference product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		demonstrating non-inferiority or superiority	
40	1	Comment: No mention of FDA guidance which does NOT require the use of animal studies Proposed change (if any): Revise paper in line with FDA guidance	Not accepted. Comment noted, but RP will outline the current European regulatory position.
40	5	Comment: Disagree that pharmacokinetic studies are necessarily required Proposed change: Change “including” to “such as”, also change “is” to “may be”	Not accepted. Since quality evaluations alone are not sufficient, additional studies are required including a human PK study.
46	4	Comment: The term “complex” in this sentence is not suitable. E.g. sucrose is not a complex carbohydrate. Proposed change (if any):	Not accepted. The term “complex” refers to the type of bonding between carbohydrate and the core.
47	4	Comment: What is meant by nano-sized colloidal aggregates? It is proposed to define nano-sized. Proposed change (if any): Add glossary for definitions and abbreviations.	Partially accepted. “aggregates” have been replaced by “structures”. A definition of nanomaterials has been provided by the European Commission on 18 October 2011. The EC has previous recognised the “special circumstances prevailing in the pharmaceutical sector”, stating that the recommendation should “not prejudice the use of the term nano when defining certain pharmaceuticals and medical devices" Commission

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
			Recommendation of 18 October 2011on the definition of nanomaterial http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF
55	4	Comment: It is preferred to change to specific cell types instead of any cell type. Proposed change (if any): (…) in specific cell types could be a safety concern.	Not accepted. There is no cell type known so far were it can be excluded that content changes of nano-sized colloidal iron will not have an impact. Therefore, a list of "specific cell types" is not possible.
56-58	5	Comment: Disagree with this statement Proposed change:Change “inability” to “difficultly” and “requisites” to “may require”	Partially accepted. “inability” has been changed to “difficulty”. “requisites” has not been changed since it is the fundamental statement of the reflection paper that data from quality, non-clinical and human PK studies are required.
58-65	1	Comment: Comments contradicted by FDA guidance which is based on research rather than hypothesis Proposed change (if any): Revise paper in line with FDA guidance	Not accepted. Comment noted, but RP will outline the current European regulatory position.
60	4	Comment: The last part of the sentence is not very clear. Proposed change (if any): (…) comparable *in vivo* fate and the resulting pharmacological and toxicological effects of these products.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
61	5	Comment: As line 40 Proposed change: Delete “in addition to human clinical PK studies”	Not accepted. A human PK study is a consistent part of the study program outlined in this paper.
64-65	5	Comment: Disagree with this statement, especially since it leaves open the possibility of a demand for full efficacy studies. Based on the change of opinion of the EMA between this RP and that of 2011 (EMA/CHMP/SWP/100094/2011) in which it was stated that non-clinical studies would be sufficient to demonstrate essential similarity – but now pharmacokinetic studies are being proposed – if this statement remains, the risk will exist that generic companies may well cancel development of iron based products, since to contemplate the door being left open to having to perform efficacy studies for a low-margin generic would be financially unacceptable. Please also see our last comment, page 6. Proposed change: Delete sentence “Further clinical studies … evidence of similarity”	Not accepted. In the revision of the RP a human PK study is an integral part of the strategy to prove similarity. With regard to human efficacy and safety studies see below.
69–77	5	Comment: These Guidelines, Note for Guidance and Reflection Paper are in our opinion of limited relevance to iron-based nano-colloidal products and listing (in this RP) should be reconsidered Proposed change: Remove those referring to biological products?	Not accepted. Iron-based nano-colloidal products are not considered as biologics and consequently guideline for biological products are not applicable to iron-based nano-colloidal products. However, it is the intention of the reflection paper that some basic principle described in guidelines for biological products should be considered for iron-based nano-colloidal products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
			Furthermore the reflection paper is one paper in a series of papers published as the European Medicines Agency's scientific guidelines on nanomedicines where it is referred to the same guidelines.
79-80	5	Comment: Disagree that pharmacokinetic studies are necessarily required Proposed change: Change “relevant quality, non-clinical and PK clinical comparative data to support” to “relevant comparative data to support”	Not accepted. Human PK study is an indispensable part of the test strategy laid down in the RP.
84	2	Comment: The possibility to provide evidence for superiority should be considered. Proposed change (if any): Similarity_-> comparability Comparative -> comparative or superior	Not accepted. The aim of the paper is to build up a strategy to prove similarity. Therefore, "similarity” is considered the appropriate wording. To prove "superiority" would require a full application.
95-97	1	Comment: How can particular quality attributes be correlated with safety *and* efficacy, especially the latter which is determined by clinical bioequivalence? Proposed change (if any): Statements should be justified and clarified	Not accepted. It might not be possible to fully evaluate the impact on safety and efficacy of each quality attribute. Therefore the reflection paper refers to a potential impact on safety and efficacy. An extensive comparability exercise with a single reference medicinal product will be required to demonstrate that the iron-based nano-colloidal product has a highly similar quality profile when compared to the reference medicinal product. Consequently data from quality, non-clinical and human PK studies are required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
97-99	2	If significantly quality differences are confirmed, it may be very challenging to claim similarity ……., a full Marketing application may be more appropriate. Comment: the nonclinical and clinical study requirements for a full application are scientifically not justified for iron replacement therapy (see above), a tailor made program seems more appropriate to save animals from unnecessary studies Proposed change (if any): full -> hybrid or even a full	Not accepted A human PK study is a consistent part of the study program outlined in this paper. Further clinical studies should not be necessary. An generic application with additional e.g. preclinical data is already considered to be a "hybrid" application, therefore no change of the wording.
100	2	Comment: The advice to minimize differences is well appreciated if the differences are supposed to negatively contribute to the risk benefit ratio of the product. Proposed change (if any): Minimize the differences -> minimize these differences provided it may be suspected to negatively contribute to the risk benefit ratio of the product.	Not accepted. It might not be possible to fully evaluate the impact on safety and efficacy of each quality attribute.
104	4	Comment: As the results will vary depending on the analytical method used it is very important to indicate the method. Proposed change (if any):	Accepted. “Results will vary depending on methods used and where ever possible two or more complementary analytical methods should be used to demonstrate comparability and ensure consistency.” has been added.
106-115	4	Comment: It is proposed to change the order.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): • the fraction of labile iron released at the time of administration and the short term stability in plasma, as labile iron has well known direct toxic effects • the physicochemical properties of the carbohydrate coating, due to: - the potential for anaphylactic/anaphylactoid reactions - the influence on the pharmacokinetics and body distribution - the influence on the safety of the product from the degradation products • the physicochemical properties of the iron and iron-carbohydrate complex, including size and variability of the iron core and size of the iron-carbohydrate complex • the stability of the iron-carbohydrate complex - as this may affect the release rate of iron and thus pharmacokinetics and body distribution	
120-140	1	Comment: These parameters are far in excess of those specified by FDA, and appear to be merely a wish-list of unvalidated assays with unknown relevance to drug safety. Proposed change (if any): Assays should be justified and validated. Should also be compared with FDA's list	Not accepted. Comment noted, but RP will outline the current European regulatory position. This section of the reflection paper addresses the characterisation of the test product. Consequently, not for all parameters validated assays are requested. It is currently not known how and what differences in physico-

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		of validated quality assays.	chemical parameters impact the clinical safety and efficacy of the drug product and thus a broad spectrum of different parameters needs to be included.
126	5	Comment: Disagree that this is an appropriate test (please refer to the accompanying letter). Proposed change: Delete	Not accepted. Labile iron is considered a relevant parameter to be addressed in regulatory submissions (see also comment on lines 120 – 140 above).
133-136	5	Comment: Disagree that this is an appropriate test (please refer to the accompanying letter (section 2.1 Quality) Proposed change: Delete	Not accepted. In-vitro release testing is considered extremely relevant during pharmaceutical development and during the comparability studies. Whether an in-vitro release assay will be requested for routine release will be decided during the approval procedure.
137	5	Comment: In our opinion this can be derived from the literature Proposed change: Delete	Partially accepted. The paragraph has been changed to: “Degradation path for the iron-carbohydrate complex”. The knowledge of degradation pathways is essential for each pharmaceutical formulation and is not limited to drug products addressed in the current reflection paper.
147	4	Comment: The quality of the starting material is crucial as it might also have an impact on safety. Therefore, starting materials of Ph.Eur. quality should be used, if possible. Proposed change (if any): (…controlled.) Starting materials shall comply with the Ph.Eur., when such monograph exists.	Accepted. The paragraph was revised: “Starting materials should at least comply with the Ph. Eur., when such monograph exists and often tighter specifications will be required for some parameters in order to match the innovator product.”

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
158-173	5	Comment: Disagree that these are appropriate tests to be applied for routine release testing since their relevance (eg appropriate values/ranges) are unknown and validated tests do not exist - please refer to the accompanying letter for details. Proposed change: Delete	Partially accepted. The sentence 'Limits for direct *in vitro* labile iron donation should be set based on batches previously demonstrated to be safe with regard to labile iron in *in vivo* studies.' was deleted. Labile iron might be determined due to its potential impact on safety. The two methods mentioned in the reflection paper are examples and not mandatory.
177	2	Comment: See rational above Proposed change (if any): Reference product. -> Reference product, provided the carbohydrate can be suspected to negatively contribute to the safety/efficacy profile of the innovator product.	Not accepted. There is no need to amend the proposed section. The comparability of the test product under development with the approved reference product should be demonstrated in the marketing authorisation application.
182-185	2	Comment: The composition of the carbohydrate could influence the iron containing nano particle both negatively or positively. Proposed change (if any): Similarity_-> comparability The provided date should be sufficient to ensure that any differences in composition of the carbohydrates have no adverse impact upon safety or efficacy of the drug product	Not accepted. "Similarity" is considered the appropriate wording. It is agreed that the provided data should be sufficient to ensure that any differences in composition of the carbohydrates have no adverse impact upon safety or efficacy of the drug product. However, this should be demonstrated in non-clinical and human pharmacokinetic studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
185	4	Comment: Even though this document is a Reflection Paper, more detailed information about the requirements to demonstrate similarity between the test and reference product should be given. Proposed change (if any):	Not accepted. The experience of regulatory agencies with marketing authorisation applications is too limited to give guidance how to demonstrate similarity/comparability. In analogy to the reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product (EMA/CHMP/806058/2009/Rev. 02) such guidance is not part of the reflection paper.
194	1	Comment: Inappropriate comment linking quality with efficacy when clinical bioequivalence is the critical criterion. Proposed change (if any): Justify comments linking quality criteria with efficacy.	Partially accepted. The word “potential” has been added.
207 - 209	5	Comment: Is this Note for Guidance directed at biotechnological/biological products really appropriate for iron-based nano-colloidal products? Proposed change: Delete	Not accepted. It is not stated that all parts of ICHQ5E are relevant in this context. It is only recommended to consider the general principles outlined in one section of this guideline.
224-289	1	Comment: 1. A recent UK Government announcement says: “Animals are only used when there are no suitable alternatives”: https://www.gov.uk/government/news/new-plan-will-work-to-reduce-use-of-animals-in-	Not accepted So far there are no suitable alternatives to reflect tissue distribution in vivo than an animal biodistribution study. The Swedish citation is a PAR which cannot be taken as scientific literature and is therefore not cited in the RP. However, the positive approval of the application in Sweden

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		research. This paper provides no justification for performing animal studies and moreover the fact that FDA does not require such animal studies for generic iron sucrose products greatly undermines the case for animal studies set out in this paper: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm297630.pdf. 2. No mention of a Swedish approval of a generic iron sucrose in which the use of a semi-quantitative determination of tissue Fe was accepted: https://docetp.mpa.se/LMF/J%C3%A4rnsackaros%20Rechon%20solution%20for%20injection_concentrate%20for%20solution%20for%20infusion%20ENG%20PAR.pdf 3. Abuse of the scientific method in that the case for using animal tissue distribution studies is based on a general hypothesis about generic nanoparticle drugs (same also for liposomal drugs). Whilst this might be a plausible working hypothesis, the whole essence of the scientific method is to perform experiments that deliberately challenge one's hypothesis. This appears not to have been done. On the other hand, FDA commissions research on such issues rather than working on the basis of	was based on an animal biodistribution study (see comment 1). In addition it is clearly stated that only one main biodistribution study will be necessary and the frame for the study design is outlined (single administration, 1-2 dose levels, 1-2 genders) There is full awareness of the lack of data in this area. This was the original reason to write a RP which is aiming to give some guidance on how similarity could be proven.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		assumptions and unvalidated hypotheses: https://www.fbo.gov/index?s=opportunity&mode=form&id=592788989854da145c8e7b6d103c898d&tab=core&_cview=1. The fact that FDA does not require such studies can be interpreted as indirect evidence that such animal studies are unnecessary. 4. Even if the tissue distribution study is deemed necessary, the methodology has not been validated, as far as can be ascertained. For example, numbers of animals, statistical methods, use of iron-deficient or –replete animals, dosing regimen, etc all have to be finalized. An applicant could be forced to undergo an almost perpetual round of exploratory studies and scientific advice in order to develop a methodology acceptable to EMA and national agencies. Proposed change (if any): The proposal for animal studies should be withdrawn.	
290-327	5	Comment: Disagree that pharmacokinetic studies are necessarily required; certainly to include details on required efficacy studies (section 2.3.2) would, as mentioned above, risk generic companies cancelling development of such products. It is agreed (lines 308 – 309) that if the data cannot demonstrate similarity then a full product development including an efficacy	Partially accepted. Human PK study is required. However, the scope of the RP is limited to similarity. Therefore efficacy studies should not be necessary. When they are necessary, a reference to an innovator product becomes dispensable.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		study would be required. This is – in our opinion – not appropriate for this reflection paper the sole purpose of which is to provide a template for the demonstration of *essential similarity of a generic product.* Proposed change: Delete at least lines 302 - 327	
293-301	2	Comment: The residence time and Cmax of the iron sugar complex in plasma could be used to estimate the risk of free iron toxicity; however, a product with decreased AUC and Cmax could be advantageous. According to present knowledge, when intravenously administered, all iron delivered by the iron sugar complex will be therapeutic active and safe provided evidence is presented that iron enters the target tissues (RES) and does not accumulate in organs irrelevant for normal iron metabolism. Proposed change (if any): The lower limit for acceptance should be deleted in line 299.	Partially accepted. The important primary parameters are free iron and transferrin-bound iron. Additional variables if justified can be added. Correlation of pre-clinical parameters/ findings with clinical investigations/parameters is a relevant topic. Not accepted. Lowering of the lower limit (CI) requires further justification.
308-309	2	Comment: The request for similarity in quality, non-clinical and human PK studies should be omitted, and changed to non-inferiority. The statement on the studies needed should refer to	Not accepted. A change to “non-inferiority” is considered not acceptable, since the topic of the RP is "similarity".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		the demonstrated differences, and drive the need for further studies. Proposed change (if any): would not -> should	
330	3	Comment: There is a very modest reference to a RMP. In our opinion, and having in mind the safety profile of iron based injectable products, some more attention should be given to this issue. Proposed change (if any):	Partially accepted. New wording of RMP section was included in RP.