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Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product

Draft

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The present document reflects the current thinking of the CHMP. The principles spelled out in this reflection paper will be reviewed in light of the experience gained with regulatory submissions and contribution from stakeholder.

Feed-back from the consultation period will be particularly important to further discuss methodological approaches for assessing comparability of products with regard to their bio-distribution in animals.

This reflection paper when finalised, will replace the Reflection paper on “non-clinical studies for generic nanoparticle iron medicinal product applications” (EMA/CHMP/SWP/100094/2011)

Comments should be provided using this template. The completed comments form should be sent to SWP-H@ema.europa.eu

Keywords	Nano-sized colloidal intravenous iron preparation, similarity with reference medicinal product, pharmaceutical, non-clinical, and clinical characterisation, tissue bio-distribution.

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Executive Summary

For the comparison of iron-based nano-sized colloidal products developed with reference to an innovator medicinal product, current scientific knowledge and regulatory experience for characterisation of nano-sized colloidal preparations indicate that quality characterisation on its own, would not provide sufficient assurance of the similarity between the two products, even if the quality tests performed show similarity. In the context of such iron based preparations, a "weight of evidence approach" including data from quality, non-clinical and human pharmacokinetic studies is required.

1. Introduction

This reflection paper discusses the data requirements for nano-sized colloidal intravenous iron-based preparations developed as a treatment for iron deficiency with reference to a nano-sized colloidal innovator product.

Iron-based products used to treat iron deficiency consist of a polynuclear iron core, generally present in the iron (III)-oxyhydroxide form, stabilised by a complex carbohydrate coating which leads to nano-sized colloidal aggregates.

When administered by the parenteral route the nano-sized iron complexes will be internalised by cells *via* the endocytic or phagocytic route e.g. via cells of the reticuloendothelial system (RES). Localisation of iron-based products to liver macrophages or hepatocytes has been noted after intravenous administration of different iron-based products.

The release of iron appears to be influenced by the size and surface properties of the colloidal iron complex and the coating. Additionally the amenability of the coating material to intracellular degradation (rate of degradation) may also influence the release of iron. Trafficking and/or accumulation of iron-based products in any cell type could be a safety concern.

The inability to fully characterise and define coated iron based particles using quality methods alone together with uncertainties on how quality attributes relate to *in vivo* performance, requisites further investigations. As a result, quality comparability and demonstration of similar plasma concentrations of iron alone, i.e. conventional bioequivalence studies in humans, would not be sufficient for the assurance of comparable *in vivo,* fate and effect of these products. Therefore, non-clinical data are required in addition to human clinical PK studies. The extent of supplementary non-clinical and clinical data required is discussed in the sections below and depends on how accurately the physicochemical and non-clinical characterisation can be used to predict differences that could influence the efficacy and safety of the product. Further clinical studies may be necessary if the results of quality, non-clinical and human PK studies do not provide sufficient evidence of similarity.

ICH and EU Guidelines

Where applicable, this reflection paper should be read in connection with the principles of relevant guidelines such as:

- ICH Q5E- section 1.4 Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (CPMP/ICH/5721/03)
- Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (EMEA/CHMP/QWP/396951/2006)
- Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product (EMA/CHMP/806058/2009/Rev. 2)

- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) Draft (EMA/CHMP/BWP/247713/2012)
- Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98/rev. 1)

1.1. Scope

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

- pharmaceutical data needed as evidence of product similarity between test and reference products to support comparative safety and efficacy
- consideration to the types of non-clinical and clinical studies that are required to support the quality data in order to demonstrate similarity

The principles outlined should also be used when considering the data requirements to support changes to the manufacture and control of existing iron based nano-sized colloidal products.

2. Discussion

2.1. Quality

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. This should include comprehensive side-by-side analyses of the proposed test and reference medicinal product using sensitive methods to determine not only similarities, but also potential differences in quality attributes. Any differences detected in the quality attributes will have to be appropriately justified with regard to their potential impact on safety and efficacy. If significant quality differences are confirmed, it may be very challenging to claim similarity to the reference medicinal product, and thus, a full Marketing Authorisation Application may be more appropriate. Alternatively, the applicant could consider adequate revision of the manufacturing process to minimise these differences.

Chemical and physical characterisation is an important means to determine the comparability of the test product to the reference product. There is a need to ensure consistent quality of these complex iron-based products through the combination of a well-defined and controlled manufacturing process and comprehensive product characterisation. The quality attributes of nano-sized iron-based products that may have a major impact on efficacy and safety include:

- 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 iron and iron-carbohydrate complex, including size and variability of the iron core and size of the iron-carbohydrate complex
- 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 stability of the iron-carbohydrate complex - as this may affect the release rate of iron and thus pharmacokinetics and body distribution

2.1.1. Quality characterisation of the test product

Correctly identifying the parameters that define relevant physicochemical properties of a nano-sized iron-based colloidal product is critical to ensure its quality. The following general parameters should be considered in the submission of all types of these products:

- Quality standard for coating materials used in the manufacture of the active substance and finished product (description, source and characterisation, manufacture, assay, impurity profile, and stability characteristics)
- Structure and composition of carbohydrate
- identification and control of key intermediates in the manufacturing process
- Particle size (and size distribution) and specific surface area of the iron core
- the fraction of labile iron released from the product when administered
- Polymorphic form of the inorganic iron compound comprising the core
- Impurities e.g. ratio of divalent and trivalent iron
- Morphology e.g. microscopic evaluation of iron distribution in the iron complex e.g. iron; surrounded by a carbohydrate coat, iron distributed through a carbohydrate matrix
- Ratio of bound carbohydrate to iron
- Particle size, size distribution, charge, of the iron-carbohydrate complexes
- *in vitro* iron release rate from the iron-carbohydrate complex in physiologically/clinically relevant media. Reliable and discriminating validated *in vitro* release methods should be developed using models that represent the extracellular (plasma/serum) release of labile iron and acid degradation kinetics
- Degradation path for the carbohydrate and the iron-carbohydrate complex
- Stability on storage of the product
- In-use stability (including after re-constitution with recommended diluents for administration) with consideration to instructions for administration in the SmPC e.g. concentration

The quality and purity of the carbohydrate starting materials is essential for the later quality of the drug product, therefore the appropriate characterisation and specification of the starting materials is considered as vital. In some cases the carbohydrate starting material is further modified. Often the carbohydrate is activated to enable binding. High processing temperatures or perhaps even moist heat sterilization of the finished product (where applied) may modify the composition of the carbohydrate. The different species of activated carbohydrate present and the levels that are present should be controlled. Functionality-related characteristics as described in the Ph. Eur. monograph 5.15 'Functionality-related characteristics of excipients' should be adequately addressed. The level of information to be provided with the relevant submission depends on complexity of the excipients. The principles of the Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product should be considered. Use of multiple suppliers for the components would require additional characterisation and comparability studies.

A list of tests to be applied routinely to the iron-based product should be defined, taking relevant pharmacopoeial monographs into account and should be based on the parameters used to characterise the formulation as described above. The analytical methods used in characterisation and control testing should be developed to ensure integrity and stability of the iron complex is maintained during analytical testing, e.g. change in size of complex on dilution.

In order to assure the safety of intravenous iron preparations with regard to labile iron it is important to develop methods to determine labile iron *in vitro* as a means to demonstrate similarity, to provide reassurance on batch release and to determine the effect of changes in production processes. Measurement of labile iron may be performed in a number of ways but two methods indicative of labile iron are as follows:

(i) Kinetic studies of iron (III) reduction by acid degradation and UV measurement. These studies should also be part of the specifications for intravenous iron preparations. Acceptance limits (both upper and lower) should be set based on the performance of batches shown in *in vitro* studies to release acceptable amounts of labile iron.

(ii) *In vitro* labile iron donation to measure direct donation of labile iron to transferrin *in vitro* by adding the intravenous iron preparation to a solution of transferrin or serum (human or animal). These studies should be used as evidence of comparability to the innovator. 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. *In vitro* labile iron donation studies should be included in the specifications for the drug product initially, until manufacturing experience increases whereby reduced testing intervals might be acceptable.

2.1.2. Establishing pharmaceutical comparability between test and reference product

The qualitative and quantitative composition of the developed product should be identical or closely match the reference product. Several different batches of the reference medicinal product should be used to provide a robust analysis and to generate a representative quality profile. The relative age of the different batches of reference medicinal product should also be considered when establishing the target quality profile.

The chemical composition of the carbohydrate should be defined and compared to the innovator product as part of the discussion of the chemical similarity of the product. Any differences in the composition of the carbohydrate coating may increase the data requirements to demonstrate similarity between the test and reference product and could be a reason for major regulatory concern when considering chemical similarity.

It is acknowledged that normally the applicant of the test product developed with reference to an innovator product will not have access to information about the manufacturing process of this reference product. Therefore, extensive investigations using state of the art characterisation methods should be applied to both products in parallel in order to demonstrate with a high level of assurance that the characteristics are comparable. Such studies should include all the relevant tests mentioned in the *Quality Characterisation* section above to adequately characterise the test and reference products. The relevance of the selected tests for equivalent performance of the drug product *in vivo* should be discussed. Any differences between the products identified in the comparability investigations should be addressed and thoroughly evaluated and justified with regard to implications on safety/efficacy.

A well-defined manufacturing process with satisfactory process controls is required in order to assure that an acceptable product is produced on a consistent basis. The critical process parameters of the manufacturing process should be defined with an appropriate control strategy.

Some critical characteristics relating to *in vivo* performance do not have one single technique available that measures this attribute accurately (e.g. particle size, surface area and surface properties). For these parameters, and where possible, consideration should be given to the use of two or more analytical methods, based on different principles to demonstrate closer comparability between the two formulations.

In addition to the characterisation studies conducted under normal conditions, comparative stress test studies of both products should be conducted in order to compare physical and chemical degradation.

All batches of the reference product used in the characterisation studies should be analyzed within their shelf-life period and should be stored under the recommended storage conditions prior to analysis.

Any differences to the reference product identified in the comparability studies should be addressed and thoroughly investigated. It is recommended to consider the general principles outlined in section 1.4 of ICH Q5E to consider further work required to demonstrate therapeutic similarity of the products.

Approaches to determining the impact of any process change will vary with respect to the specific manufacturing process, the product, the extent of the manufacturer's knowledge and experience with the process and development data provided. Comparative investigations should be undertaken when a change is introduced into the manufacturing process during development but also after marketing authorisation, e.g. for scale up.

2.2. Non-Clinical

2.2.1. Methods of analysis

For comparison to a reference product, analytical methods developed and validated to quantify analytes in blood/plasma and in tissue will be necessary. Careful attention should be paid to the impact of all sample processing procedures during the course of method development, employing methodologies to verify the suitability and interpretability of all bioanalytical results.

The lower limits of quantitation and recovery in plasma, tissues and, where relevant, in particular tissues of interest e.g. see table 1 below, should be stated.

2.2.2. Bio-distribution studies

Non-clinical studies should be planned with an intention to show comparability between the test and reference product. Studies should be conducted in compliance to GLP, unless appropriately justified (e.g. necessity to use specialised test systems). Non-clinical studies should be undertaken with test and reference products that have been characterised appropriately (see section 2.1 above). The test product should be produced using the final manufacturing process and would ideally be from the same batch used for the pivotal clinical studies.

When administered by parenteral route, iron nanoparticles are generally thought to be recognised by the RES (liver, spleen, lymph nodes, bone marrow, lungs, etc.), and undergo phagocytosis by macrophages but may also be handled by endothelial or epithelial cells (such as hepatocytes) through endocytosis. Internalisation of iron will vary according to the surface properties of the nanoparticles and to the protein adsorption (corona formation). Consequently, different ways and different velocities of phagocytosis mediated by an opsonisation-like phenomena will occur which most probably will result in a significant inter-species variability.

Some pharmacokinetic aspects of nanoparticular iron products with regard to their performance in humans can be modelled by animal and cell-based models. Nevertheless, distribution studies in a relevant animal model are essential to evaluate distribution, metabolism and excretion of these

nanoparticles and of their *in vivo* degradation or solubilisation products. Particular emphasis should focus on the distribution, accumulation and retention in at least three compartments; plasma, reticular endothelial system (RES) and target tissues/organs (Table 1). These studies should provide pivotal evidence of the comparability of the *in vivo* disposition of nanoparticular iron products, as it is not possible to fully explore distribution in humans from blood/plasma data alone.

Distribution should be evaluated in rodents starting with a dose finding study to establish appropriate dose levels which can be accurately measured (sensitivity of the method) and to determine the best sampling strategy of time points to reflect the incoming iron and release of iron from the respective tissue. Reasonable time points should be carefully evaluated and should be selected to cover the entire concentration-time profile for all tissues of interest. Previous knowledge of biodistribution of the reference product may also be used for the design of the study. Early sampling time points (e.g. less than 24h), should be included to ensure comparability with regard to early clearance by the reticulo-endothelial system.

A main distribution study including one or two genders with one to two dose levels and single administration may be sufficient.

Table 1. Relevant compartments for the distribution of intravenous iron- based nanoparticles for iron deficiency

1. Plasma (or serum) and red blood cells
2. RES: macrophages e.g. in spleen, liver (Kupffer cells)
3. Target tissues 3.1 Pharmacological target tissues e.g. bone marrow 3.2 Toxicological target tissues e.g. kidney, liver (hepatocytes), lungs, heart

Selection of target organs and tissues for the measurement of analytes should include at least the organs identified from the distribution pattern of the reference product and the test product for the above three compartments (see Table 1). For the RES compartment, the spleen is the recommended organ for the measurement of iron concentrations. Other methods to measure distribution such as the use of imaging technologies may be acceptable if shown to be appropriate.

As the coated nanoparticles will be gradually degraded, total iron measurements will not reflect the physiological level of iron or the oxidation status. However, the time-dependent release of the stored iron from a given compartment reflects the product degradation process and its biological relevance. Therefore, measurement of the time-dependent overall iron content in different tissues may be sufficient to reflect the degradation profile of the nanoparticle.

In this context, distribution of the test product to each compartment should be understood at least on the cellular level in addition to the tissue or organ level. It is evident that cellular distribution of iron is important i.e. whether distribution in the liver is actually to Kupffer cells or to hepatocytes.

Iron concentration in tissues may be measured for example via mass spectrometry ICP-MS or atom emission spectrometry ICP-AES or even via photometry. In addition, histological detection of iron in the tissues should be considered as accompanying approach. In any case, the method used does not have to be extremely sensitive since the increase in iron due to i.v. application is expected to be quite substantial. Presenting the data in terms of the amounts per gram of tissues as well as the presentation of the data in terms of the percentage of the dose (with a mass balance recovery) is encouraged.

Development of additional and more accurate analyses of the degradation process of the nanoparticles is encouraged. For example cell or tissue culture systems could be used for mechanistic purposes to study the uptake of the nanoparticles and their degradation or solubilisation products into the RES, macrophages or hepatocytes/Kupffer cells.

There is insufficient regulatory experience with non-clinical bio-distribution studies at present to recommend specific decision criteria for comparability of tissue distribution. However, it is strongly recommended that criteria for comparability in distribution and clearance in comparison to the reference product are clearly defined and justified by the sponsor in advance of the study. It is proposed that quantitative statistical approaches developed for showing similarity or equivalence are used. The clinical implications of any noted differences in tissue distribution between test and reference product should be carefully discussed.

Toxicity studies are not sensitive enough to demonstrate similarity between test and reference product. Therefore they are not useful for this purpose and would result in unnecessary use of animals. In case of specific safety concerns, appropriate safety endpoints included in the design of the bio-distribution study may be sufficient to address these concerns.

2.3. Clinical

2.3.1. Pharmacokinetics studies

The pharmacokinetics of the iron-based nano-colloidal product should always be compared with the innovator's product. Single-dose parallel or crossover design is recommended. The primary variables are the AUCt and Cmax of baseline, corrected total- and transferrin-bound iron. The analytical methods should be developed and validated to confirm absence of impact from sample processing procedures and employing methodologies to verify the suitability and interpretability of all bioanalytical results.

If a replicate design is applied then confidence limits for Cmax can be extended as described in the Guideline on the Investigation of Bioequivalence. Otherwise the 90% confidence interval of the baseline corrected values should be in 80-125% range. The sampling period should be sufficiently long to demonstrate that the iron levels return to the previous baseline level. Results should be discussed in relation to *in vitro* quality control tests (see section 2.1.1 (ii)).

2.3.2. Efficacy and Safety studies

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.

Differences which may impact the efficacy and safety of the test product compared to the reference product would be a cause of regulatory concern.

Major differences seen in quality, non-clinical and human PK studies would indicate a lack of similarity and further evidence provided by therapeutic equivalence studies would not address these deficiencies.

Should the results of any of these studies show minor differences between the two products, a therapeutic equivalence study might be necessary to address their impact on efficacy and safety.

When considering a clinical trial to address differences, the applicant is strongly advised to seek scientific advice for the choice of end points and study design. The CT would ideally be at least 3 months in duration and performed in a group of patients with a similar aetiology for their anaemia, e.g. patients with chronic renal failure. End points to be considered include:

- Ferritin
- Transferrin saturation
- Haemoglobin
- Total iron dose administered over study
- Total EPO dose administered over study
- Safety end points in such a study will have to concentrate on short term safety, looking at the commonly seen adverse events and also markers that could indicate an adverse safety profile. These could include:
  - Anaphylactoid reaction rate
  - Non-transferrin bound iron (NTBI)
  - Overall adverse event rates
  - Markers of oxidative stress and free radical activity

2.4. Pharmacovigilance / Risk Management Plan

Differences in anaphylactic/anaphylactoid reactions rates would not be identifiable through usual comparability studies. The RMP should be developed to take this into account. Long term safety issues will also not be measurable in a clinical study that could reasonably be conducted. Novel imaging techniques are available that can look at cardiac and liver iron deposition, which can occur when the products are used over a long period of time. The concerns over chronic increase in oxidative stress and iron deposition should be considered in a comprehensive risk management plan, including existing knowledge on the safety of the reference product, as only long term and systematic follow-up will elucidate the full safety profile of the products.