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Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
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1. Introduction

The "engineered" surface of a nanomedicine product[1] interfaces with the biological environment, the precise nature of which will depend on the proposed clinical application, and the route of administration e.g. blood plasma in intravenous delivery. Many nanomedicines approved as products and/or undergoing development include as an integral component of their design either a non-covalent or covalently bound coating. The coating is typically used to minimise aggregation and improve stability (e.g. iron solutions for treatment of anaemia)[1] or, in certain cases, to minimise reticuloendothelial system (RES) clearance after intravenous administration with the aim of prolonging plasma circulation time and providing an opportunity for improved disease-specific targeting (e.g. PEGylation as applied to PEGylated liposomes)[2]. Coatings have also been used to improve haemato-compatibility and limit antigenicity. These phenomena can arise due to the inherent physicochemical composition of the nanomedicine or to the surface adsorption of biomolecules from the biological environment to which they are exposed, e.g. plasma protein interaction to form what has been called the "protein corona".

It is evident that presence of a coating has the potential to impact on the critical properties of the nanomedicine in terms of safety and efficacy. The physico-chemical nature of the coating, the uniformity of surface coverage, and the coating stability (both in terms of attachment and susceptibility to degradation) will govern the pharmacokinetics, the bio-distribution of the product and its intracellular fate. In addition, the infusion-related reactions observed clinically for certain coated nanomedicines (e.g. iron solutions and PEGylated liposomes) may be due to the physico-chemical properties of the coating material, specific bio-molecular interaction with the coated nanomedicines (e.g. complement activation) and/or cell interaction. In some cases a coating material may elicit new biological responses, not observed for either the coating material alone or the unmodified surface alone.

On-going research is rapidly leading to the emergence of more sophisticated surface modifications and certain nanomedicine products are already in clinical development (e.g. liposomes designed for receptor-mediated targeting). In this regard, the use of ligands (e.g. proteins) to promote receptor-mediated targeting underline the need to carefully consider the chemistry used for their attachment. Control of ligand orientation is important as heterogeneity will impact on the PK and bio-distribution of the nanomedicine. In addition, random orientation may itself lead to a new pattern of biomolecule association with the nanomedicine surface which may in turn impact on its safety.

The above observations underline the need for careful consideration of both covalently bound and non-covalently associated coatings in terms of their potential impact on the safety and efficacy of nanomedicine products. This paper highlights issues that require consideration during the development and lifecycle of coated nanomedicine products designed for parenteral administration. It should be read in connection with the following documents:

- Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator product EMA/CHMP/SWP/100094/2011
- Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product EMA/CHMP/806058/2009/Rev. 02
- Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products EMA/CHMP/13099/2013

[1] Next Generation nanomedicines and nanosimilars: EU regulators' initiatives relating to the development and evaluation of nanomedicines; Falk Ehmann, Kumiko Sakai-Kato, Ruth Duncan, Dolores Hernán Pérez de la Ossa, Ruben Pita, Jean-Marc Vidal, Ashish Kohli, Laszlo Tothfalus, Alan Sanh, Sandrine Tinton, Jean-Louis Robert, Beatriz Silva Lima and Marisa Papaluca Amati; Nanomedicine (2013) 8(5), 849-856

2. Discussion

2.1. General Considerations

General issues to consider during the development of nanomedicine products that include a covalent or non-covalent coating are:

- The effect of the coating on the product stability (e.g. polymer-coated liposomes)
- The effect of the coating on the product pharmacokinetics and bio-distribution (e.g. polymer-coated liposomes)
- The effect of the coating (physico-chemical characteristics) on biomolecule interactions (including opsonisation), and cellular interaction in the biological environment relevant to proposed use
- The potential for the coating material to elicit non-specific (typically charge-dependant and hydrophobic interactions) and/or receptor-mediated cellular targeting (e.g. polysaccharides/glucose receptors). For example, alteration in the pattern of liver cell localisation (Kuppfer cells: hepatocyte ratio) has been reported for iron solutions containing different coatings.
- The potential of the coatings to affect the metabolic pathway of the entrapped active moiety

2.2. Product characterisation

Consideration of quality, non-clinical and clinical data will play an important role in the definition of the critical product characteristics of a coated nanomedicine. The following are important:

- Complete characterisation of the coating material, including its composition and control.
- In the case that the coating agent itself (or by addition of a targeting ligand) includes a complex molecule (e.g. protein or antibody) its consistency and reproducibility may require additional characterisation
- Complete validation of the coating step, including definition of the chemistry involved in the adherence of non-covalent coatings or conjugation of covalently bound coating material. Also important to define is the physico-chemical nature of the surface to which the coating adheres or is covalently bound.
- It is important to consider the potential impact of surface coverage heterogeneity of the coating on the safety and efficacy of the product.
- The orientation and conformational state of any ligand should be defined in those products involving an active targeting residue at the surface
- Stability of the coating (stability during storage and in use).The coating has the potential to detach and/or may be degradable.
- In vitro determination of the physico-chemical stability of the coating in respect of proposed use, under conditions relevant to the route of administration, pharmacokinetics and bio-distribution, and target disease.
- Premature detachment of the coating material and/or degradation of the coating has the potential to reveal new functional groups on the nanomedicine surface. The potential consequences in terms of efficacy and safety should be considered.

- In vivo impact of different coating materials/surface coverage on PK and bio-distribution should be considered
- Furthermore, it is important to consider the bio-distribution of the released coating material and its metabolic fate.

Control and assurance of the quality of coated nanomedicine products cannot just be based upon a set of test specifications on the final product. It requires a well-defined and controlled manufacturing process supplemented with a suitable control strategy (appropriate in process controls for the critical steps of the manufacture of the product including the coating process).

3. Conclusion

When developing coated nanomedicines careful consideration should be given to the potential impact of the coating on the efficacy and safety profile of the product. This information is critical when evaluating studies designed to support first in man clinical evaluation, pre- and post-authorisation manufacturing changes for a coated nanomedicine, and for the demonstration of similarity for a follow-on coated nanomedicine product, developed with reference to an innovator product.

4. References

[1] European Medicines Agency. Reflection paper on non clinical studies for generic nanoparticle iron medicinal product applications. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/04/ WC500105048.pdf

[2] European Medicines Agency. Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/ WC500140351.pdf