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First Asia Pacific Educational Workshop on
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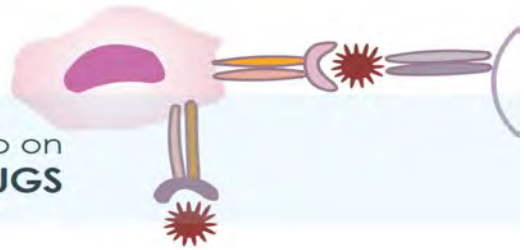

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First Asia Pacific Educational Workshop on
NON-BIOLOGICAL COMPLEX DRUGS

Non-clinical Aspects of the Development of Non-Biological Complex Drugs (NBCD) Regulatory Position in the European Union

Beatriz Silva Lima

Kuala Lumpur, 8 October 2013

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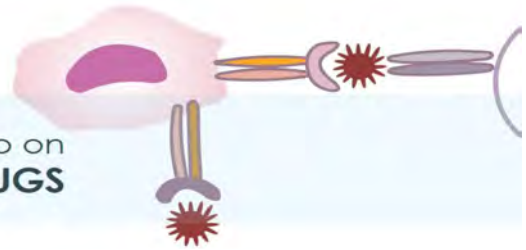
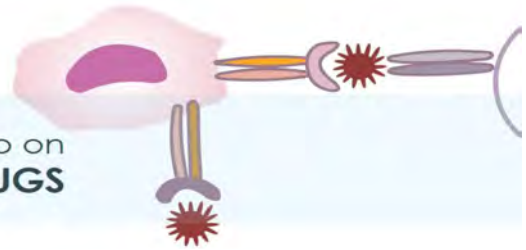


Disclaimer NDA

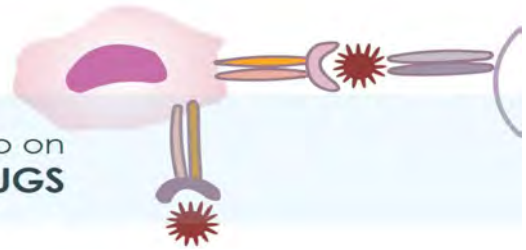
- The views and opinions hereby expressed reflect only my personal opinion and not the views of institutions or organisations with which I am or have been affiliated in the past or present



Aspects of Definition of NBCD

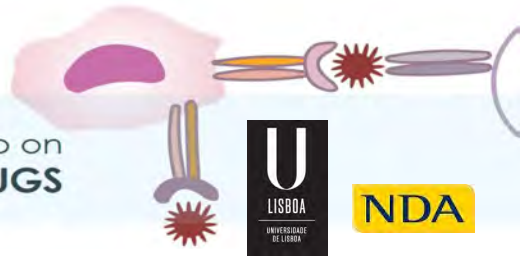
Their active substance, like for biologics, consists of different (closely related) Structures

- Fully quantitation and characterization of these structures using (physico)-chemical analytical means is not *(yet)* possible
- Examples are *(nanoparticle-based MPs)*: iron sucrose, block copolimer mycelles, liposomes, transferosomes (?), etc



EU:EMA Actions Towards NBCD

- EMA Ad-Hoc Nanomedicine Expert Group, (2009) (SWP/QWP/EMA coordination)
- Nanomedicines International Working Group (2009) (EMA, FDA, MHLW, Health Canada…)
- EMA Drafting Group on Nanomedicines (2011)

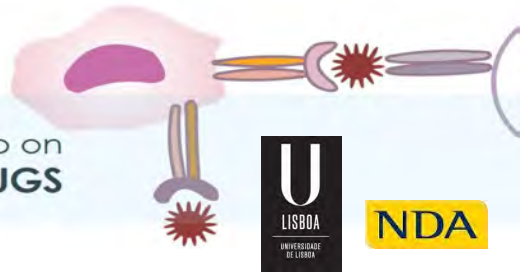


EMA Ad-Hoc Nanomedicine Expert Group, (2009)

Some of the Tasks Acomplished

- **Areas covered by the term 'nanomedicines':** review of current working definitions in the EU and major categories of nanotechnology applications in medicinal products

- **Workshop on Nanomedicines 26-27 April 2010**
  - What are nanomedicines?
  - Products on the market / Products in the pipeline
  - Regulatory gaps
  - Other priority areas to be addressed
- **1st International Workshop on Nanomedicines, September 2010.**



Regulatory Thinking on Nanosized Formulations

- New NP / **New AS**
- "Known" NP / **New AS**

- New NP / Known AS

- "Known" NP /Known AS

Regulatory Thinking on Nanosized Formulations

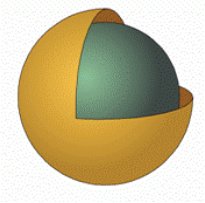
- New Active Substance (New or known NP):

Existing Paradigms Sufficient to Address Efficacy and Safety (with technical adaptations)

  - Covering Quality/Efficacy/Safety (NC+C) of the new API
  - Covering Quality/Efficacy/Safety (NC+C) of the new NP
  - And Full characterisation/**justification** of the NBCD formulation (particle, active substance and complex).

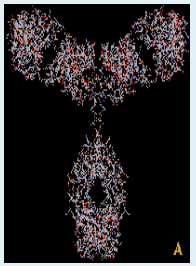
Regulatory Thinking on Nanosized Formulations

- Known Active Substance
  - New (NP) formulation: Safety and Efficacy to be reevaluated – Proof of Concept to be provided
  - Known NP ("generic formulation") : existing paradigm for comparability NOT applicable



Generics vs Biologics vs NBCD

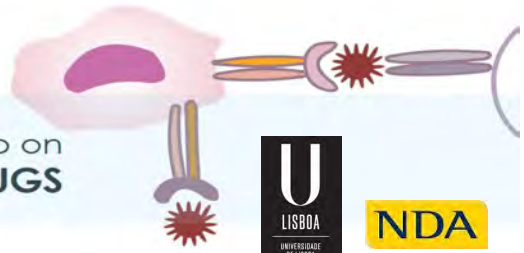
- Data requirements for Generics: Quality and Bioequivalence
- Proof of biosimilarity for 2 Biologics can be derived from (at least)
  - Quality characterization (eg Mabs)
  - reduced nonclinical (in vitro?)
  - Comparative human kinetics/efficacy/safety



- ***For NBCD More Extense Exercise may be needed (eg in vitro and in vivo NC studies)***
  (like the more complex biologics??)

Starting Point: Factors of relevance for the activity of NBCD

- The Nanoparticle (NP)
- Active Substance (AS)
- The particle Coating
- The Complex

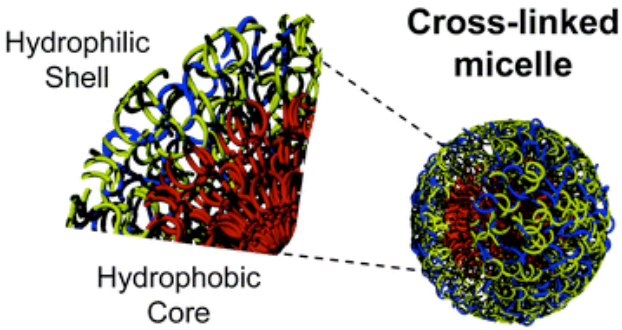


Nanoparticle-Related Factors

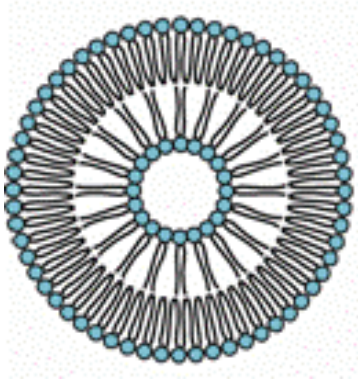
- **Type and Composition vs Fate**
- **Physicochemical properties vs**
  - Cellular/subcellular distribution of the NP
  - Organ / tissue / cellular distribution of the AS
- **(Intrinsic) Biological Activity / Consequences for the Active Substance**

All aspects need to be understood and characterised

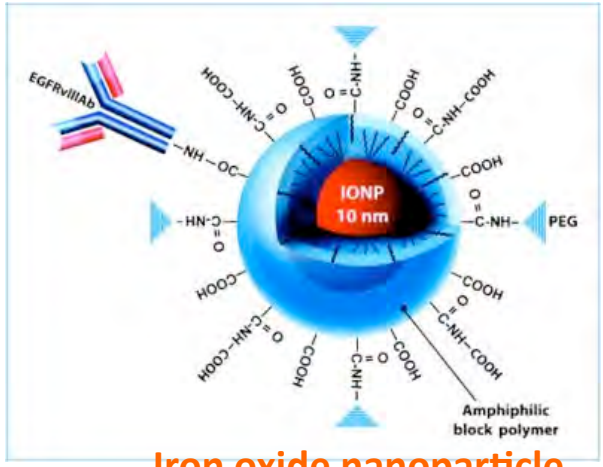
A Multiplicity of Nanoparticles Are Possible



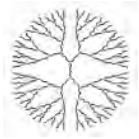
micelles



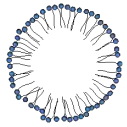
Liposomes



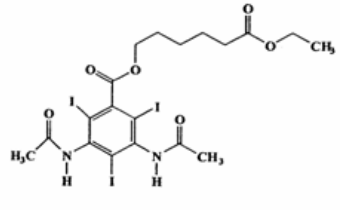
Iron oxide nanoparticle



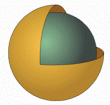
Dendrimers



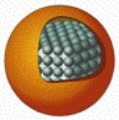
Nanoemulsions



Nanocrystals

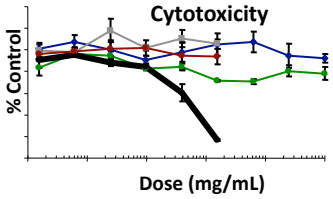


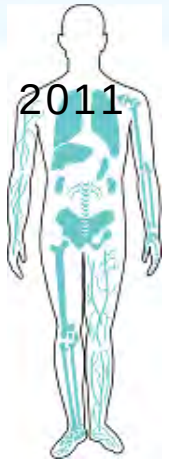
Gold nanoshells

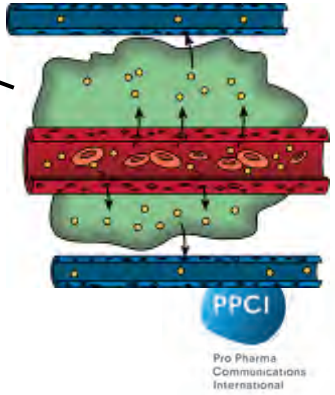


Quantum Dots

Nanoparticle & Biocompatibility (MacNeil, CRS Annual meeting, Washington 2011







(+)
Hi
Zeta Potential
0
Hydrophobicity
(–)
Low
1 nm
220 nm
Size
(Rigid Core)

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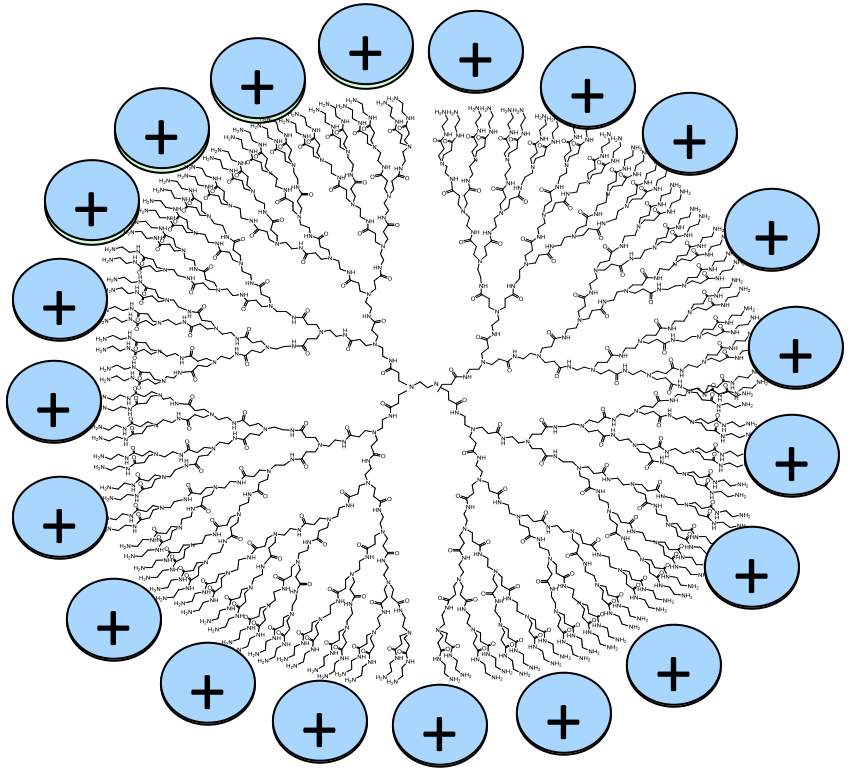
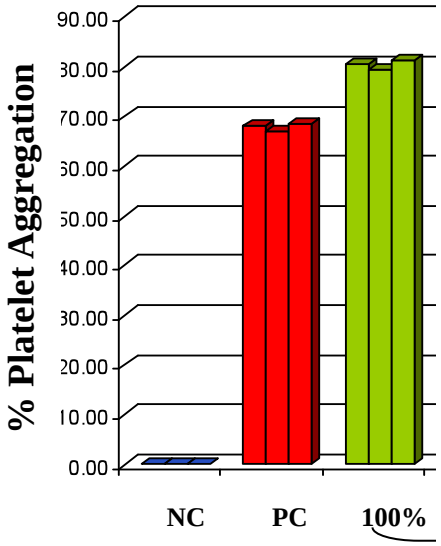
McNeil, (2009), Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 1:264-271.

Impact of Surface Charge





McNeil, (2009), Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 1:264-271.

A Learning Process!

➔The better the knowledge on
Quality attributes – Biocompability relationship

➔The higher the understanding on potential impact of any changes on the NBCD Activity & Targeting properties

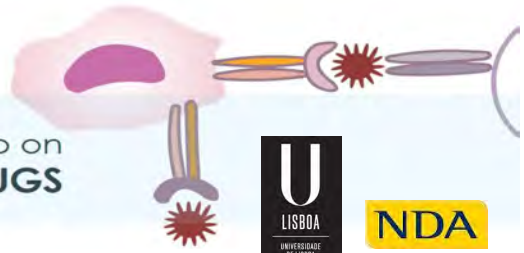
CHMP Assessment Report on Doxorubicin SUN

www.ema.europa.eu/.../WC500112957.pdf

-Two original tissue distribution studies submitted with the Marketing Authorisation Application. Considered defficient!

- -on doses,
- -analyte choice,
- -methods of data analysis,
- - Interpretation of results

-Two additional studies conducted and submitted on D120 LOQ response, and two on day 180 LOQ response



CHMP Assessment Report on Doxorubicin SUN

www.ema.europa.eu/.../WC500112957.pdf

Review of Studies conducted

-errors in the method of calculation of plasma and tissue AUC in the four studies

-New calculations, revised reports, additional documents on software re-submitted by Applicant

-New assessment made

-Tissue distribution of Dox SUN vs Caelix

Assessment outcome: Concerns on reliability of data persisted
Equivalence not considered as proven

Iron Sucrose

A number medicinal products contaning iron oxide nanoparticles have been approved as "follow on" products (controversial data published in the literature)

Roth et al, Translational Research 2008;151:36-44 (BfArm)

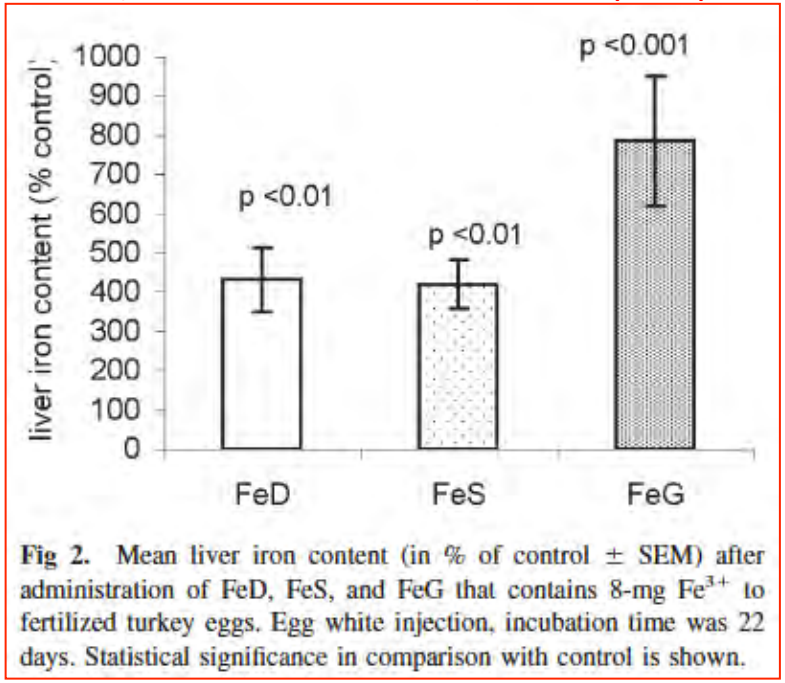


Fig 2. Mean liver iron content (in % of control ± SEM) after administration of FeD, FeS, and FeG that contains 8-mg Fe^{3+} to fertilized turkey eggs. Egg white injection, incubation time was 22 days. Statistical significance in comparison with control is shown.

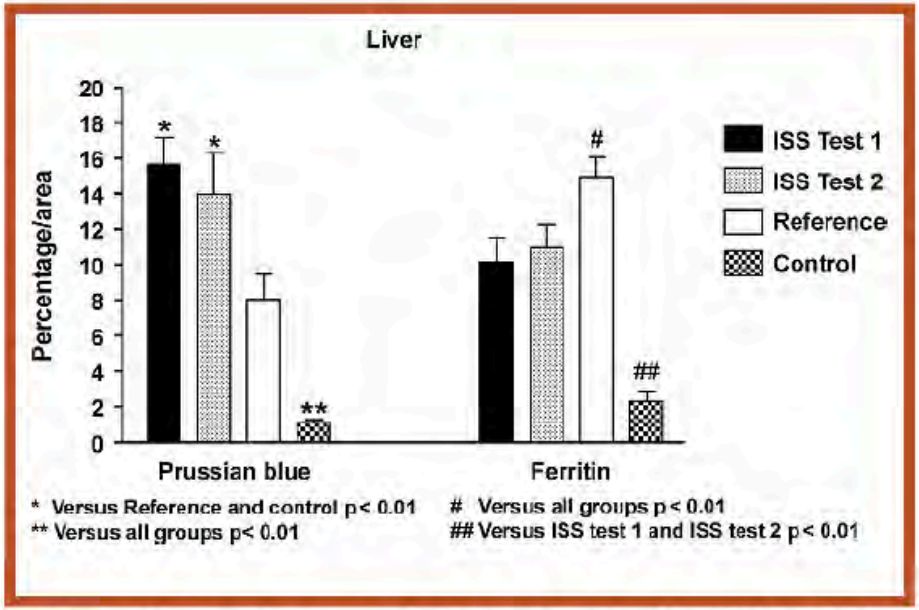
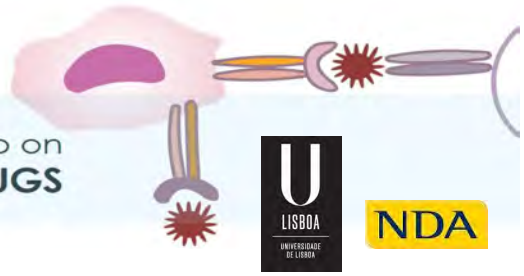


Fig. 6: Bar charts and micrographs showing Prussian blue staining for iron deposits and ferritin immunostaining for stored iron in liver samples taken from the ISS test 1, ISS test 2, reference and control groups on day 28.

Toblli et al, Arzneimittelforschung 2009;59(4):176–190
Followed by Inflammation & Allergy - Drug Targets, 2012, Vol. 11, No. 1



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17 March 2011
EMA/CHMP/SWP/100094/2011
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications

Draft Agreed by Safety Working Party	February 2011
Adoption by CHMP	17 March 2011

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.

Keywords	*Iron nanoparticles, non-clinical comparability studies, tissue distribution*

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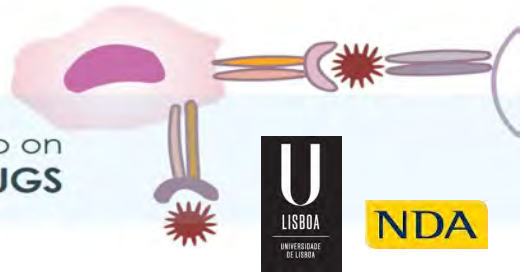
1 25 July 2013
2 EMA/CHMP/SWP/620008/2012
3 Committee for Medicinal Products for Human Use (CHMP)

4 Reflection paper on the data requirements for intravenous 5 iron-based nano-colloidal products developed with 6 reference to an innovator medicinal product

7 **Draft**

CHMP Nanomedicines Expert Group discussions	January to October 2012
Draft Agreed by QWP	November 2012
Draft Agreed by Safety Working Party	July 2013
Adoption by CHMP for release for consultation	25 July 2013
Start of consultation	15 September 2013
End of consultation (deadline for comments)	28 February 2014



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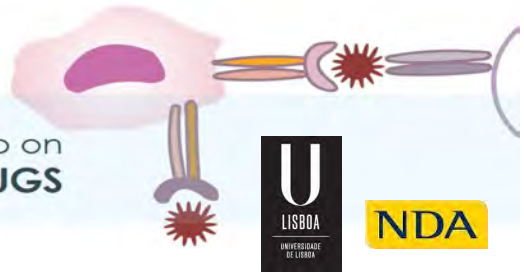
22 May 2013
EMA/325027/2013
Committee for Medicinal Products for Human Use (CHMP)

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

Agreed by Nanomedicines Drafting Group	October 2012
Adoption by CHMP	27 June 2013



(Draft) Reflection Papers on the Data Requirements for

- IV iron-based nano-colloidal products developed with reference to an innovator medicinal product (EMA/CHMP/SWP/62000/8/2012; for comments up to Feb 2014
- Surface coatings general issues for consideration regarding parenteral administration of coated nanomedicine products; published August 2013
- Data requirements for IV liposomal products developed with reference to an innovator liposomal product (CHMP/806058/2009/Rev.02; Published Feb 2013.
- **Development of block-copolimer-micelle medicinal products (Draft) CHMP/13099/2013; for comments up to July 2013**
- Non-clinical studies for generic nanoparticle iron medicinal product application

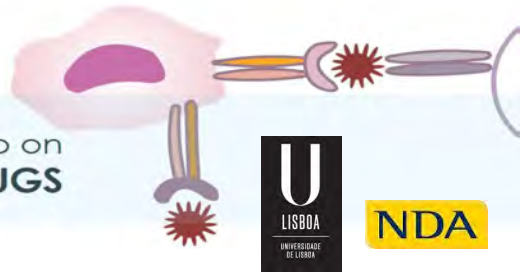
NOTE:

- **Reflection Papers are NOT Guidelines**
  - Are aimed at providing transparency to stakeholders on current regulatory thinking!

- **Their Publication is NOT mandatory**
  - **BUT is advisable for transparency**

Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product

- ***Assists in the generation of relevant data to support the MA of a liposomal product developed with reference to an innovator one .***
  - ***-quality,***
  - ***-non-clinical***
  - ***-clinical***
- Assists on decisions on the **Necessity of pre-clinical and clinical studies** (including 'usual' bioequivalence studies) **and circumstances which may allow to waive certain studies.**



Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product

The principles outlined might also apply to other novel types of "liposome-like" and vesicular products which may be under development, by iv or other routes of administration

Conclusion section:

- Limited regulatory experience
- Recommendations given are general
- Companies are advised to seek product-specific scientific advice on specific questions on the data requirements to demonstrate comparability of liposomal formulations

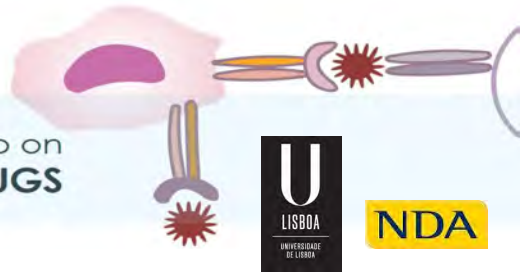
Reflection Paper on Requirements for Intravenous iron-based Preparations for Iron–Deficiency Anaemia With Reference to a Nanoparticle Innovator Product

Scope of the Reflection Paper

- **Assist in the generation of relevant data** on quality, non-clinical and clinical to support a marketing authorisation/variations e.g. change in manufacturing process, specifications and critical analytical methods of I.V. iron-based preparations for iron-deficiency anaemia with reference to a nanoparticle innovator product.
- **Facilitate a decision on the type of data needed :**
  - Pharmaceutical
  - non-clinical and clinical
- The principles outlined… may also be used in the development of new intravenous iron-based preparations for iron-deficiency anaemia .

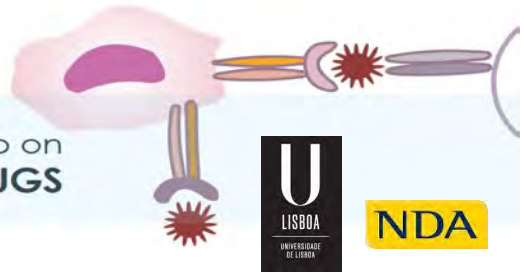
Relevant aspects of nonclinical testing

- Similar plasma concentrations may not lead to similar activity
- Comparative Characterisation of cellular and subcellular distribution may be needed.
- Understanding of quality attributes impacting on distribution and activity



Critical PK Properties versus Toxicity Aspects:

- Potential for rapid clearance by the (RES)
- Size-related elimination: (e.g. renal)
- potential for instability in the circulation resulting in premature dissociation and/or premature drug release.
- Potential for accumulation in solid tumours due to (EPR effect) or other target tissues
- Their specific physicochemical properties size, charge, composition, as important determinants of safety and efficacy.
- Certain “empty” particles may display inherent biological activity (e.g. modulation of membrane transporters such as p-glycoprotein).



Common Discussions in the Reflection Papers

Analytical Methods

- Need for validated analytical techniques for measuring during in vivo PK and biodistribution studies:
  - the particle containing entrapped (or covalently bound) drug
  - the "empty" particle or particle component-drug conjugates
  - the released active substance and the active substance metabolites
  - depending on the the particle, it may also be necessary to monitor the particle-related metabolites

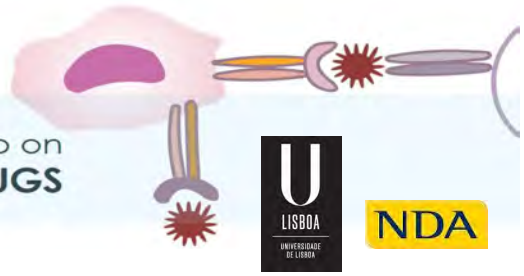
Common Discussions in the Reflection Papers

- in vitro / in vivo Pharmacodynamics (Comparative)

- Pharmacokinetics and Biodistribution Studies (multiple time points) (Comparative)

- Biodistribution of NBCD product in relevant organs (safety and efficacy) (Comparative)

- in vivo Toxicology studies, need and format (comparative)



EUROPEAN MEDICINES AGENCY
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1 17 January 2013
2 EMA/CHMP/13099/2013
3 Committee for Medicinal Products for Human Use (CHMP)

4 Joint MHLW/EMA reflection paper on the development of 5 block copolymer micelle medicinal products

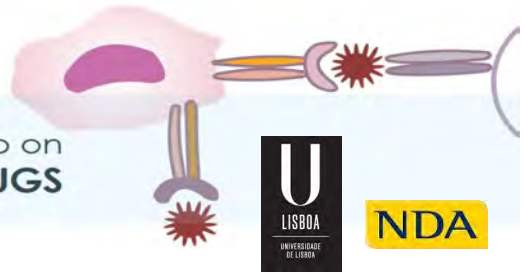
6

Agreed by Nanomedicines Drafting Group	October 2012
Adoption by CHMP for release for consultation	17 January 2013
Start of public consultation	1 February 2013
End of consultation (deadline for comments)	1 July 2013

Block Copolymer Micelle (BCM) Products

- Several block copolymer micelle products are currently in pre-clinical or in clinical development, for example, products containing anti-tumor agents and proteins.

- As block copolymer micelle products are of nano-scale size, contain more than one component, and are purposely designed for specific clinical applications they may be considered as nanomedicines

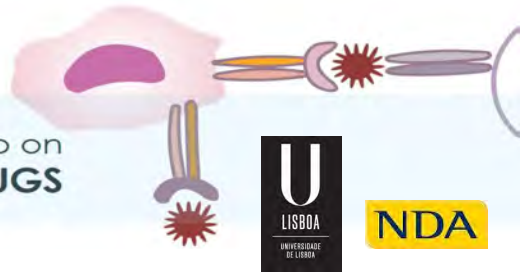


General considerations

Non-clinical studies

- **Significant changes in PK** characteristics can occur when an active substance is administered as a BCM product, i.e.
  - , i.e. volume of distribution and clearance may be changed,
  - half-life prolonged and tissue distribution changed
- **Significant changes in PD and safety** of the active substance can also occur when it is administered as a BCM product.

- Moreover, it has been noted that certain BC (not containing an active substance) **can display inherent biological activity**, which would have an impact on clinical efficacy and/or safety.

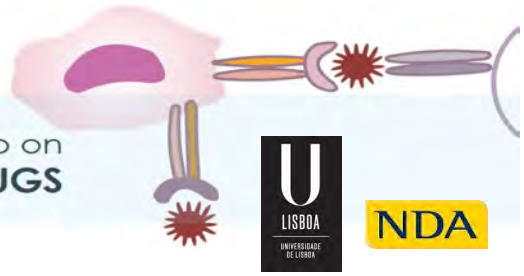


Non-clinical studies

Toxicology

- For the non-clinical evaluation of toxicities of block copolymer micelle products, the recommendations in the ICH safety guidelines especially of S4, S6(R1) and S9 and M3 (R2) should be followed.

- Relevant toxicity studies of the block copolymer micelle product should be conducted to assess both the toxicological profile and exposure-response relations according to the ICH safety guidelines.



Non-clinical studies

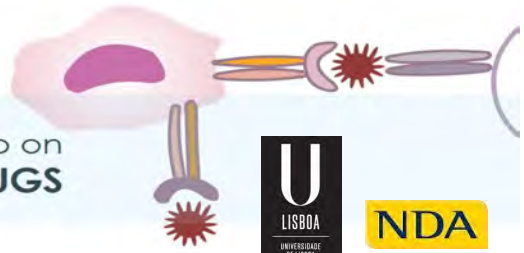
Toxicokinetics

- In addition to blood, plasma, or serum concentration, the active substance should be measured in the target tissue(s) and toxicologically relevant organs related to proposed clinical use.

Non-clinical studies

Additional studies

- Depending on the physicochemical and/or pharmacokinetic characteristics of the block copolymer micelle product and/or the block copolymer used for its manufacture, target organ function evaluation may be necessary.
- Certain nanomedicines have the potential to induce infusion reactions. Studies designed to investigate complement activation, hematotoxicity, antigenicity, and/or immunotoxicity (ICH S8) should be considered depending on the characteristics of the block copolymer micelle product. .

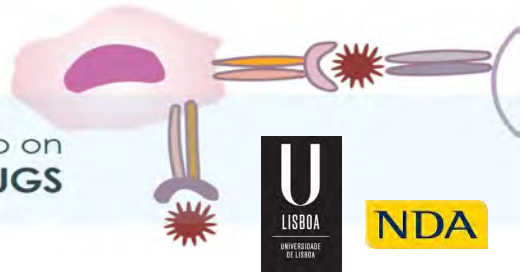


Consideration for FIH studies with BCM products

- Potential critical quality attributes for each block copolymer micelle product should be identified and used to evaluate consistency
- Consistency of the quality attributes should be confirmed between the products used for non-clinical studies and those for first-in-human studies,
- and test procedures should be established before commencement of first-in-human studies.
- If the manufacturing process used to prepare block copolymer micelle product for non-clinical studies is changed before first-in-human studies comparability should be demonstrated or otherwise justified

Difficulties ....

- Insufficient knowledge on the impact of quality attributes and modifications on the activity of the products.
- In vivo studies carry insufficient power to detect (small) differences (against 3Rs principles)
- Use of more advanced/sophisticated techniques difficult to impose (e.g. microscopy, imaging, etc) for "generic-like" developments
- Predictive approaches based, e.g. on modelling may be needed



Some Forefront Science Needs to Solve Current Problems

- Further Clarification of Quality/Biology relationships
- Inteligent NC data to complement Quality is needed
- POC studies to confirm Quality Claims (e.g. dose reduction, toxicity change, biodistribution aspects)
- Will NBCD good pilot cases for modelling exercises?


Thank
YOU!