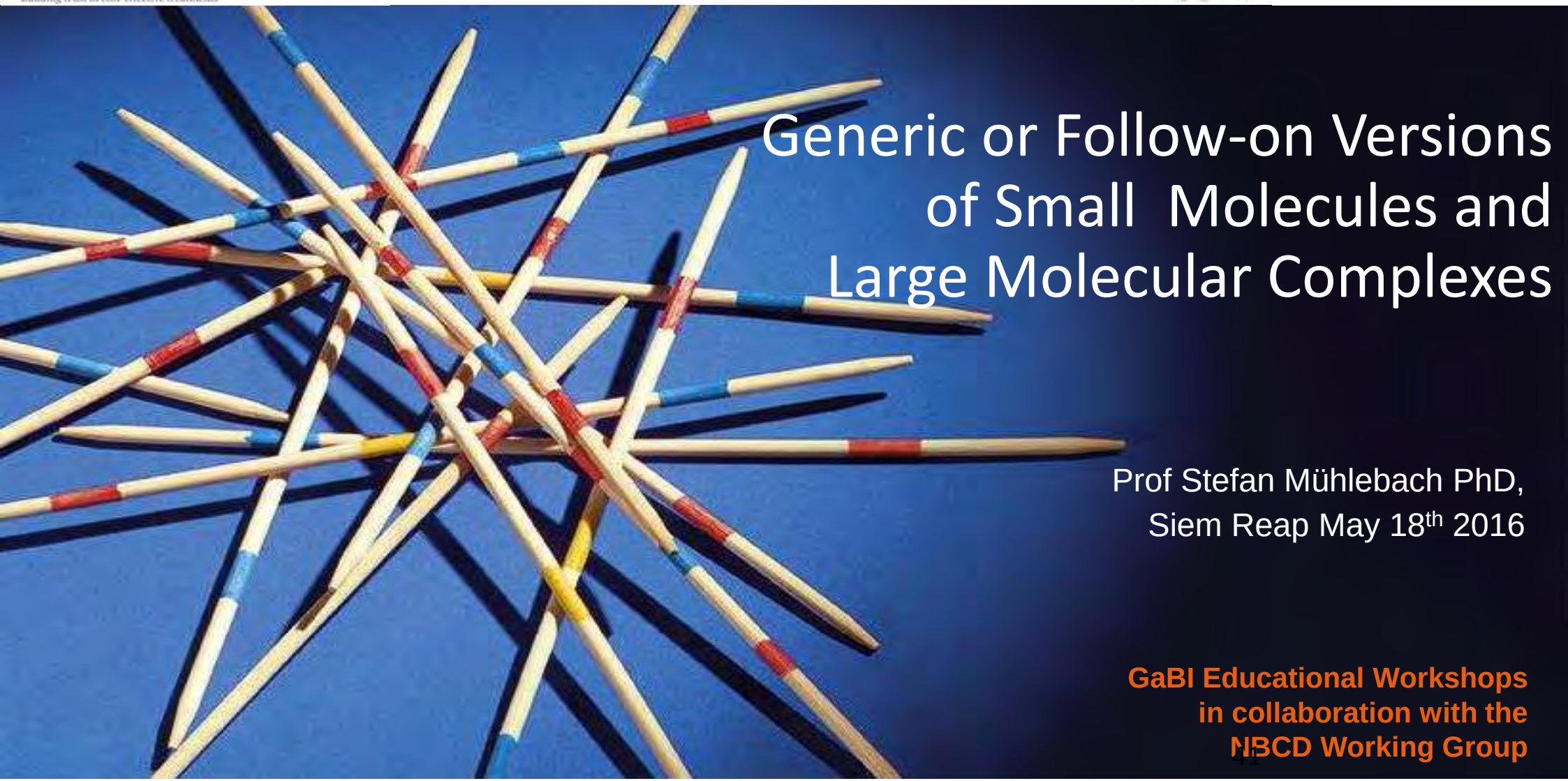
GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

PPCI
Pro Pharma Communications International

Non Biological Complex Drugs working group

lygature

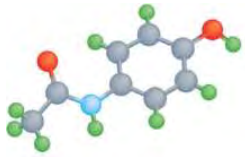


Generic or Follow-on Versions of Small Molecules and Large Molecular Complexes

Prof Stefan Mühlebach PhD,
Siem Reap May 18th 2016

GaBI Educational Workshops in collaboration with the NBCD Working Group

Large molecular complexes follow on versions: Similar but not the same: equivalence matters



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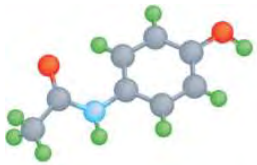
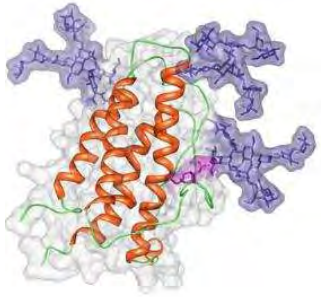


Small single molecule
(Acetaminophen: 151g/Mol)

"Generic"
(identical copy)



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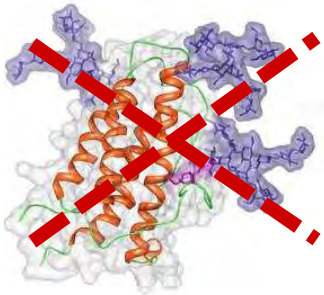

Large, complex molecules (mix)
(Mol weight range EPO: 34-39 kD)

"Similar"
(**non identical** copy)

Table 1: Substantial differences between conventional and complex drugs

	Conventional Drugs	Complex Drugs
Size	Small (single molecule)	Large (mix)
Structure	Simple, defined	Complex, defined by the exact manufacturing process
Modification	Well defined	Many options
Manufacturing	- Predictable chemical process - Identical copy can be made	- Difficult to control from starting material to final API - Impossible to ensure an identical copy
Characterization	Easy to characterize fully	Cannot be characterized fully (mixture of related molecules)

Schellekens et al. Poster AAPS (FIP) 2010:
Non-biological complex drugs:
How to show therapeutic equivalence
http://www.aapsj.org/abstracts/AM_2010/R6341.pdf

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Therapeutic equivalence of generic products

Generic paradigm for conventional drugs (EMA, FDA):

✓ Pharmaceutically equivalent (identical API/formulation): **the same**

✓ Bioequivalent in healthy subjects (volunteers): **comparable AUC**

⇒ **comparable PK / PD / safety**

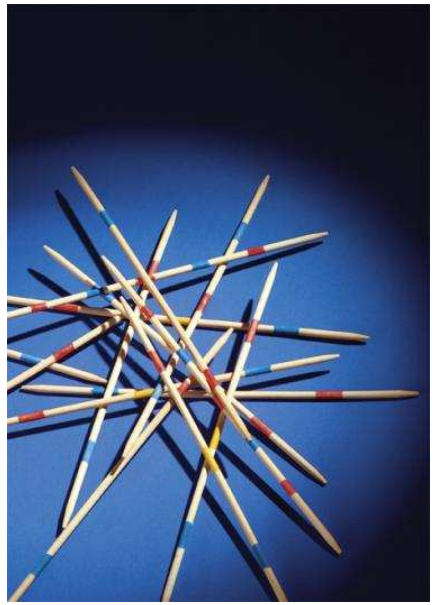
Generics interchangeable substitutable	Clinical efficacy and safety studies not required

Therapeutically equivalent

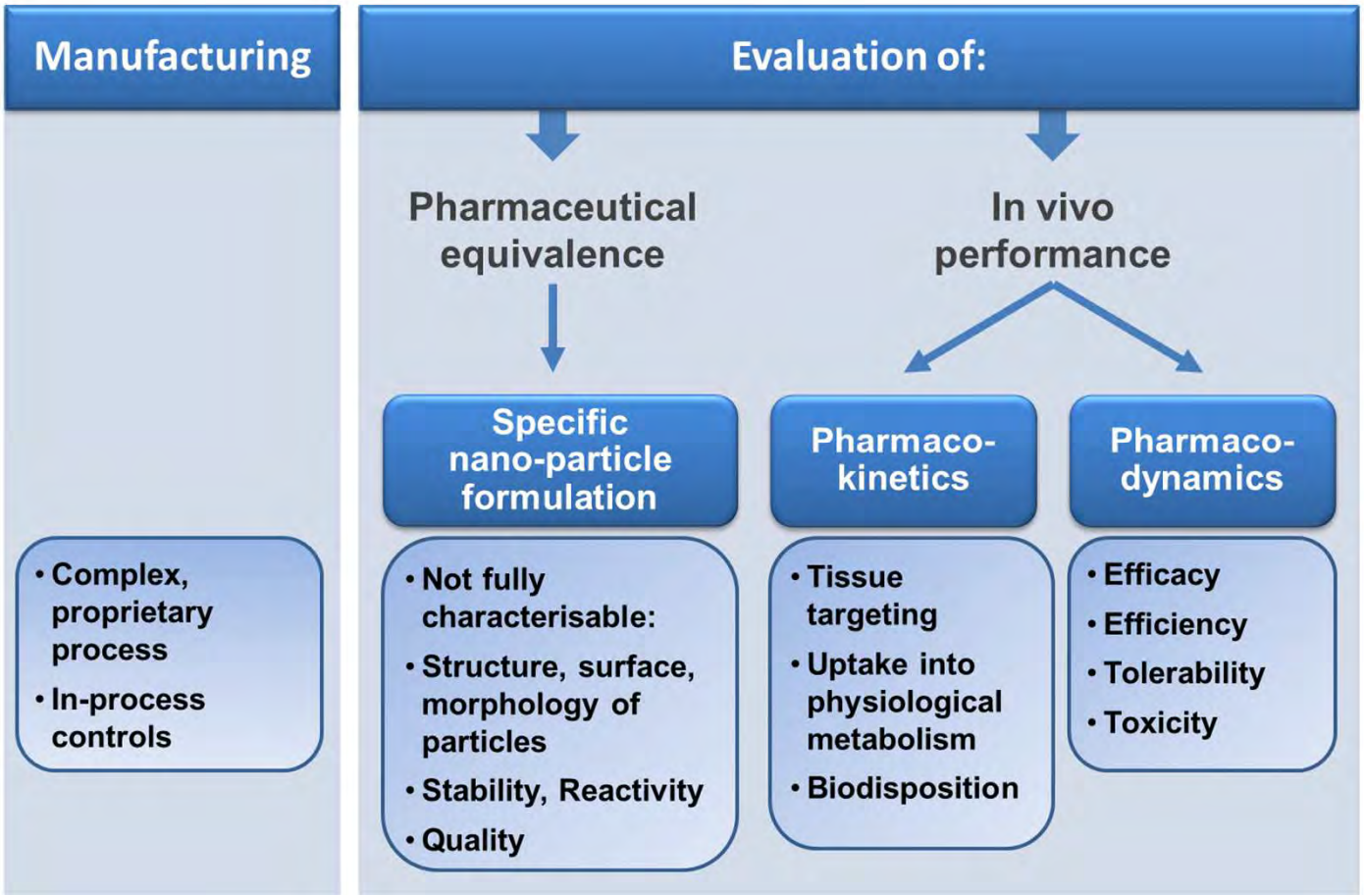
The *generic paradigm* is **only applicable to fully characterized active pharmaceutical ingredients** (small molecules)!

Non-biological complex drugs (NBCDs)

- Synthetic, non biological large molecular medicinal products
- Not homo-molecular, closely related, nanoparticular, polymeric structures
- The entire product is the pharmaceutical active ingredient
- **Can't be fully characterized** by physicochemical analytical means
- Unknown structural elements that might impact the therapeutic performance: **clinically meaningful differences in similars?**
- Variable immunogenicity
- The profile of the product dependent on the multi-step manufacturing process: composition, quality and in vivo performance (nano!)



From manufacturing to efficacy and safety



Representatives of NBCDs

Iron carbohydrates (A)

Colloidal IV iron preparations comprising a **polynuclear** iron-oxohydroxide core complexed with a carbohydrate to stabilize and prevent iron toxicity and facilitate uptake and processing in macrophages

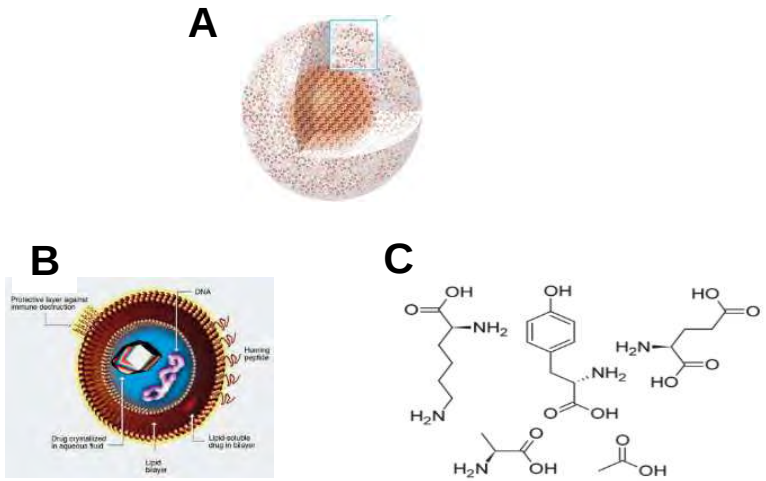
Liposomal drugs (B)

Nanoparticular vesicles composed of phospholipid bilayers that can be synthetized from a great **variety of lipid constituents**

Glatiramoids (C)

Synthetic **copolymer** mixtures with immunomodulatory activity containing four L-amino acids (glutamic acid, alanine, lysine, tyrosine)

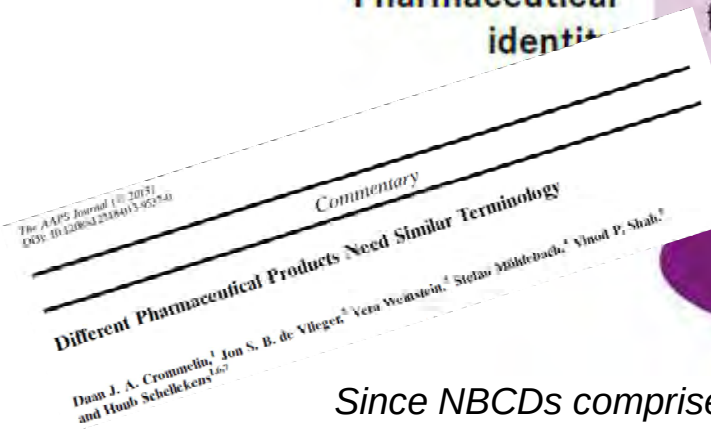
adopted from 17th EAHP conf. 2011 poster PHC030



A Iron sucrose (iron carbohydrates)
B Liposomal drugs
C Glatiramoids

Importance of terms for follow-on versions

Category	Small molecule	Biologic	Non-biological complex drug
Example	acetylsalicylic acid	epoetin alpha	iron sucrose
Pharmaceutical identi…	fully characterizable	not fully characterizable	


Commentary

Different Pharmaceutical Products Need Similar Terminology

Daan J. A. Crommelin, Jon S. B. de Vlieger, Vera Weinstein, Stefan Mühlebach, Vinod P. Shah

Generic

Biosimilar/ Biologic follow on

Similar

*Since NBCDs comprise a class of molecular complexes that largely differ from small molecular weight medicinal products, it is important to differentiate between **intended copies** of NBCD (copies of non-complex medicinal products) and **generics** already in the terminology.*

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Borchard G. et al. Reg Toxicol Pharmacol 2012;64:324-8
Crommelin DAJ. et al. AAPS J. 2014;16(1):11-14.

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Comparability / equivalence of IV Fe colloidals

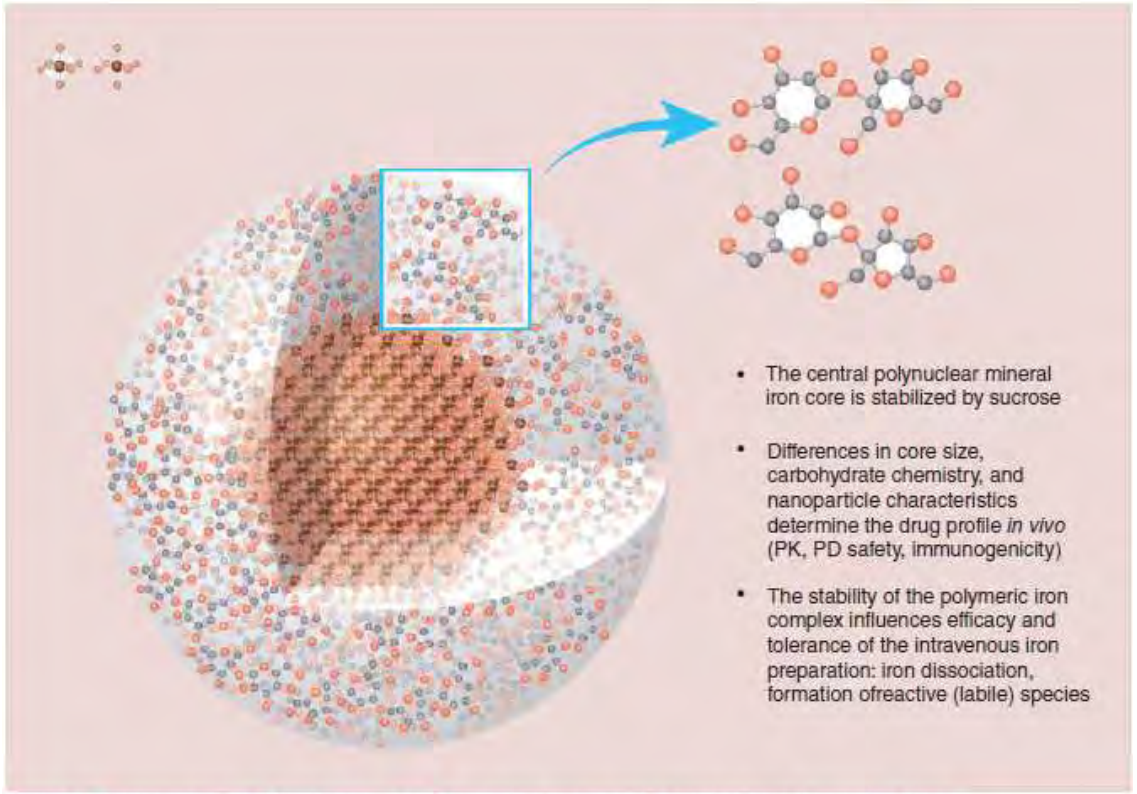
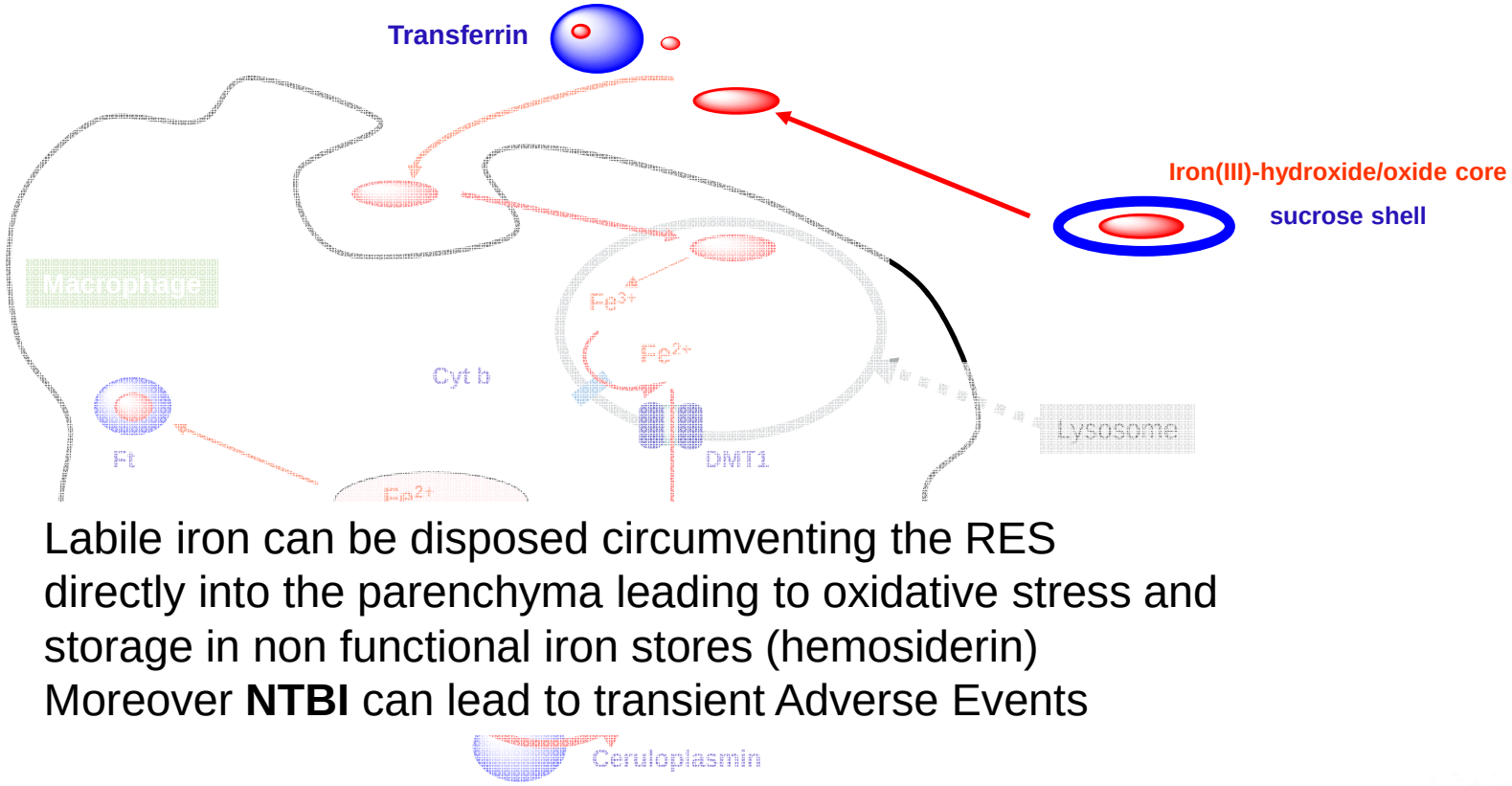


Figure 3. Representation of iron sucrose as a typical nanoparticular nonbiological complex drug.
PD: Pharmacodynamics; PK: Pharmacokinetics.

Mühlebach S. et al. Nanomedicine 2015;10(4):659-74

Innate immune system (RES): Uptake of iron nanoparticles by monocytes



Labile iron can be disposed circumventing the RES directly into the parenchyma leading to oxidative stress and storage in non functional iron stores (hemosiderin)
Moreover **NTBI** can lead to transient Adverse Events

DMT1: Divalent metal transporter 1; LIP: labile iron pool; Ft: ferritin.

Targeting IS_{org} vs. ISS in non-anemic rats

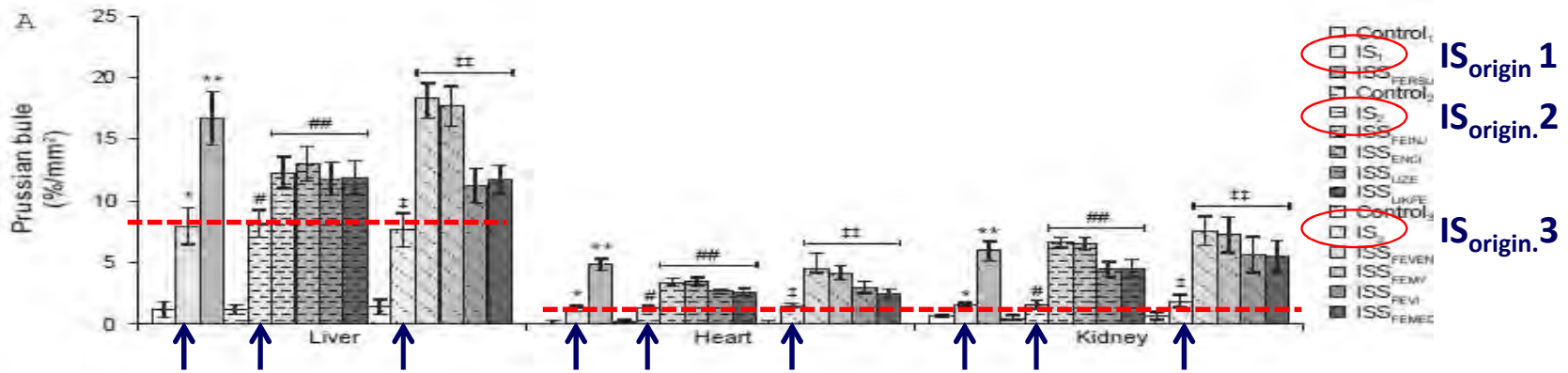
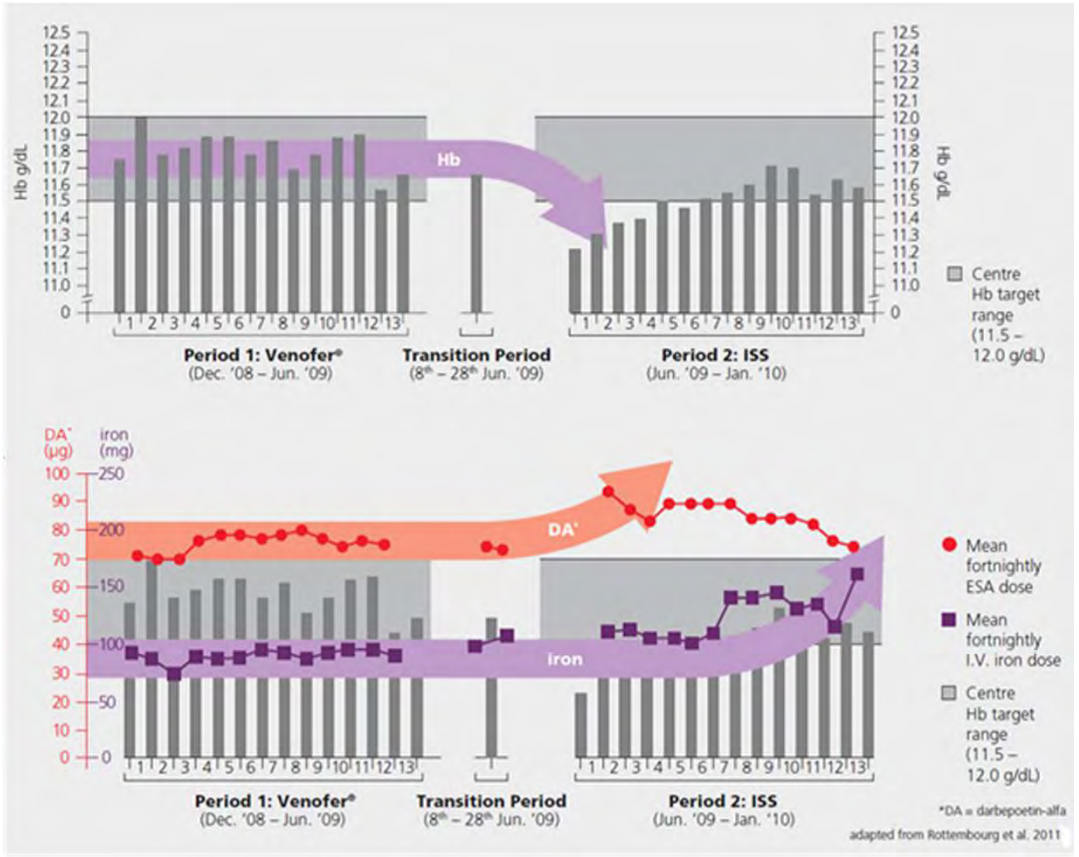


Fig. 1 Immunostaining on day 29 a Prussian blue detectable iron(III) deposits b Ferritin deposits

Toblli J et al. Biometals 2015;28(2):279-92

Switching from IS $_{orig}$ to an ISS$_{authorized}$ in stable HD patients (n=75)



Adapted from Rottembourg et al. Nephrol Dial Transplant 2011;26:3262–3267
Rottembourg et al. J. Kidney 2016;2:110. doi:10.4172/jok.1000110 (n=66 switched back, Fe, ESA need restored)

The switch from ISS to IS_{orig} reduces IV iron and EPO dosing in HD-patients

34.3% less IV iron dosing with IS_{orig}

=

960 mg i.v. iron less per HD-patient/year with IS_{orig} **p<0.001**

12.5% less ESA consumption after switching to IS_{orig}

=

One syringe of epoetin-α calculated as weekly dose of 3'000 IE/0,3 ml (25,2 µg/0,3 ml)

190.8 µg ESA less per HD-patient/year after switch from ISS to Is_{orig} **p<0.001**

- A prospective, observational multi-centric study comparing two subsequent treatment periods of 13 months each, including 342 HD pats.
- Hb levels were stable over two treatment periods of 13 month each
- TSAT went up from 28.6±7.2% to 30.7±7.6% (**p<0.001**) after switch to IS_{orig}
- Ferritin increased from 507ng/ml to 579 ng/ml (**p<0.001**) after switch to IS_{orig}

Agüera ML, PLoS One10(8):e0135967 doi:10.1371/journal.pone.0135967

lygature

NBCDs: «similars» are not «the same»: therapeutic equivalence matters

Learnings from parenteral nanomedicines and nano-colloidal iron follow-on products:

How similar is enough?
Totality of evidence
Interchange / switch?

- Quality (at best but not a full picture)
- Pharmaceutical comparability (manufacturing, stress test)
- Non-clinical (biodisposition, targeting)
- Clinical
- PV

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