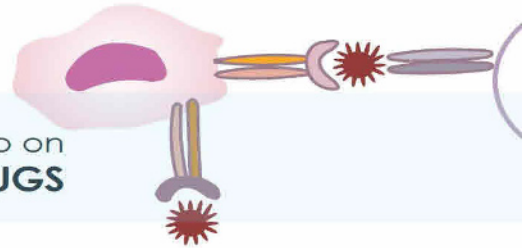


Professor Stefan Mühlebach, PhD, Switzerland

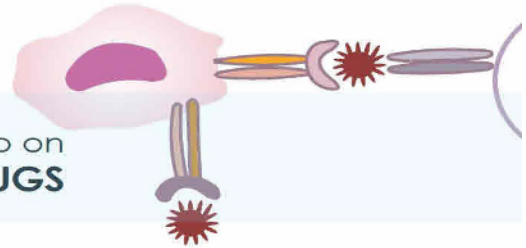
- Scientific Director GRA, Vifor Pharma Ltd (Switzerland)
- Chair of the WG “Non-biological complex drugs”, c/o TIPharma (The Netherlands)
- Professor of Pharmacology and Hospital Pharmacy, Dept. Pharmaceutical Sciences, University of Basel

stefan.muehlebach@viforpharma.com

‘Generic’ or follow-on versions of small molecules, biological, and non-biological complex drugs: The scientific and regulatory gap when similarity but not sameness applies

Professor Stefan Mühlebach, PhD

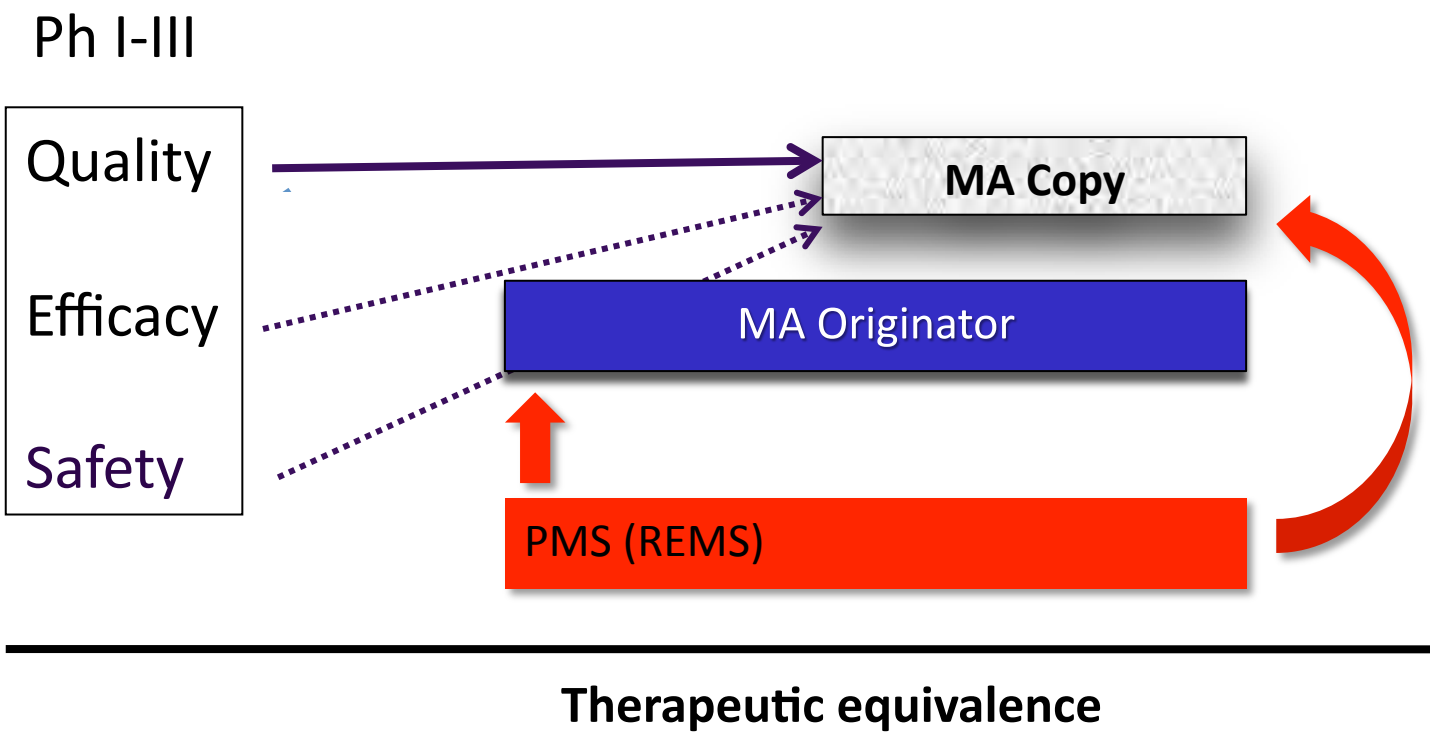
8 October 2013



Content

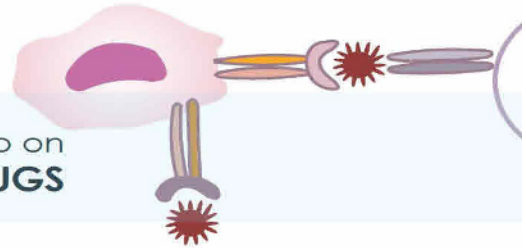
- Abbreviated evaluation of follow-on MP
- Non-biological complex drugs (NBCD) (nano-) similars
- Regulatory challenges for approval (comparability, interchange/substitution)
- Conclusions

Market Access: Originator and Follow-on Copies



Therapeutic equivalence
exchangeable
substitutable
(comparability)

***PMS**: Post Marketing Surveillance*
***REMS**: Risk Evaluation & Mitigation strategy*

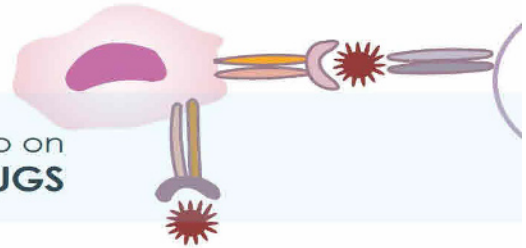


Therapeutic Equivalence (comparability) of Small Molecular Drug Copies

- **Conventional generic paradigm** (EMA, FDA):
- Pharmaceutical equivalence (identical API…)
- Bioequivalence in healthy subjects: comparable PK ($CI_{90\%}$ range 80-125%)
- Known mode of action

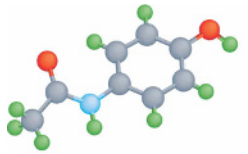
No clinical efficacy and safety studies required

Generics
(interchangeable)
No clinical testing needed



Approval of "Generic" Medicinal Products:

Generic paradigm



Small molecules drugs (m.w. <500*)*

e.g. ASA

Fully characterized

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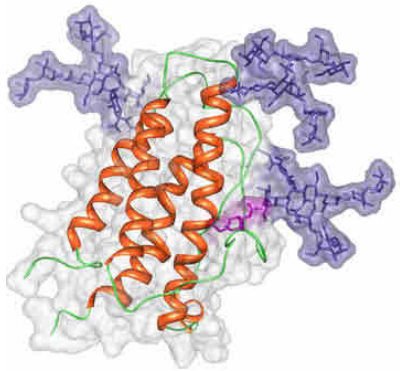
Biosimilar approach



Complex (biological) drugs

(m.range 5-150kDa)

e.g. EPO

Not fully characterized

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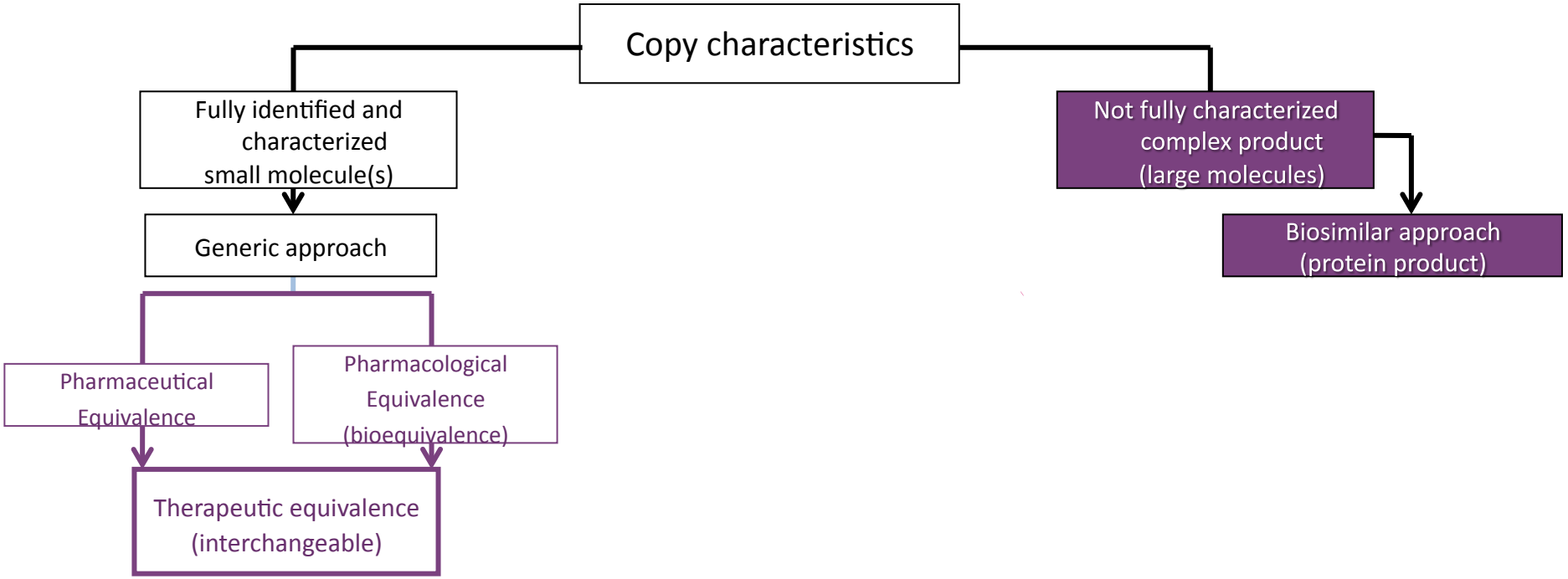
Authorization of a Bological Copy: the EMA Similar Approach



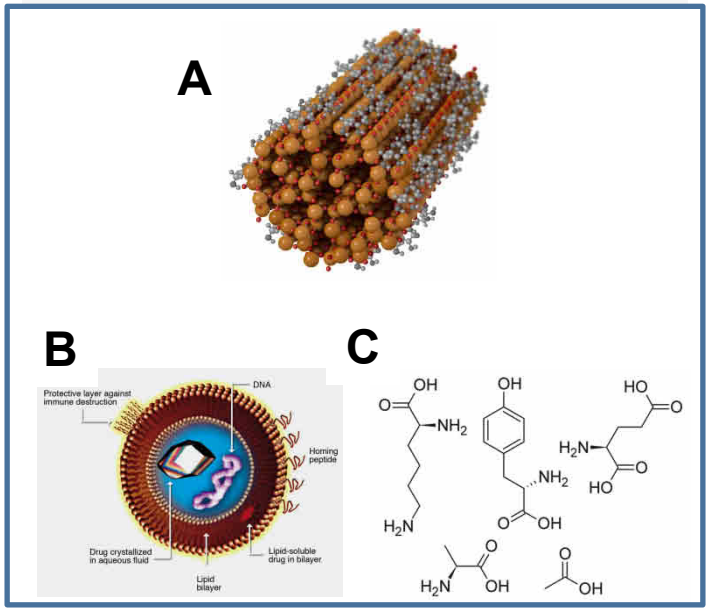
Adopted from Regul Toxicol Pharmacol 2011;59:176-183;
RTP 8(50)973-977 (Therapeutic equivalence of complex drugs)

Non-Biological Complex Drugs (NBCD)

Synthetic, not a biologic,
large molecular nanoparticle,
polymeric (mix) product

- The entire complex is the active pharmaceutical ingredient
- The properties **cannot be fully characterized** by physicochemical analysis
- The **manufacturing process is fundamental** to create the product and difficult to control

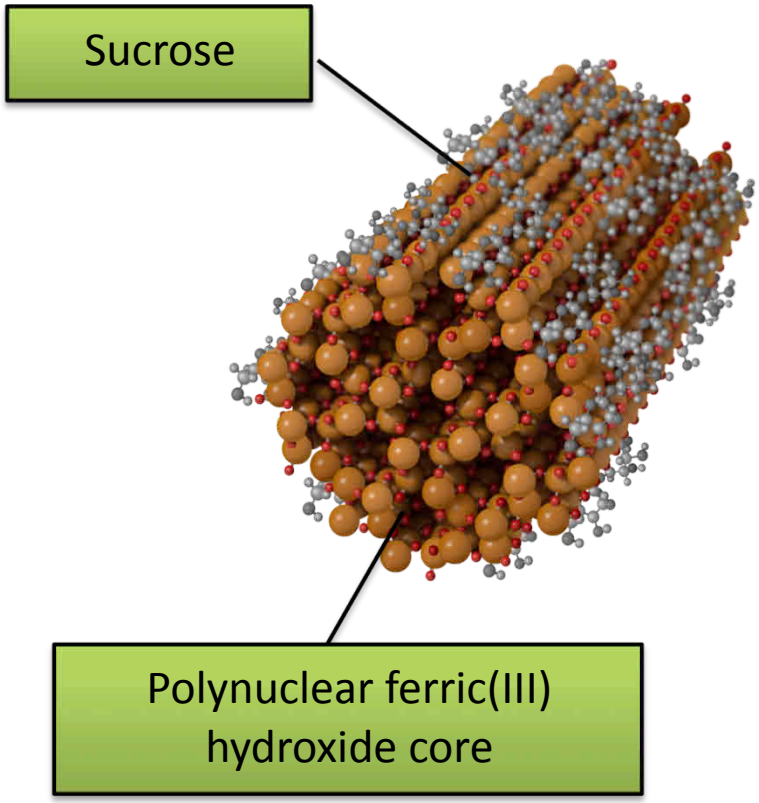
Adapted from poster PHC030 17th EAHP conference 2011



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

AAPS-J online. How to regulate NBCD and their follow-on versions

Structure: The Carbohydrate Shell of i.v. Irons



- The mineral central core containing polynuclear ferric(III) hydroxide iron is **stabilized** by interactions with the polysaccharide.
- **Differences** in core size and carbohydrate chemistry and (nano-) **particle characteristics** determine pharmacologic (PK, PD) and biologic differences (safety, immunogenicity).
- The stability of the iron complex influences **efficacy and tolerance** of the i.v. preparation: (iron dissociation ROS formation, NTBI etc.).

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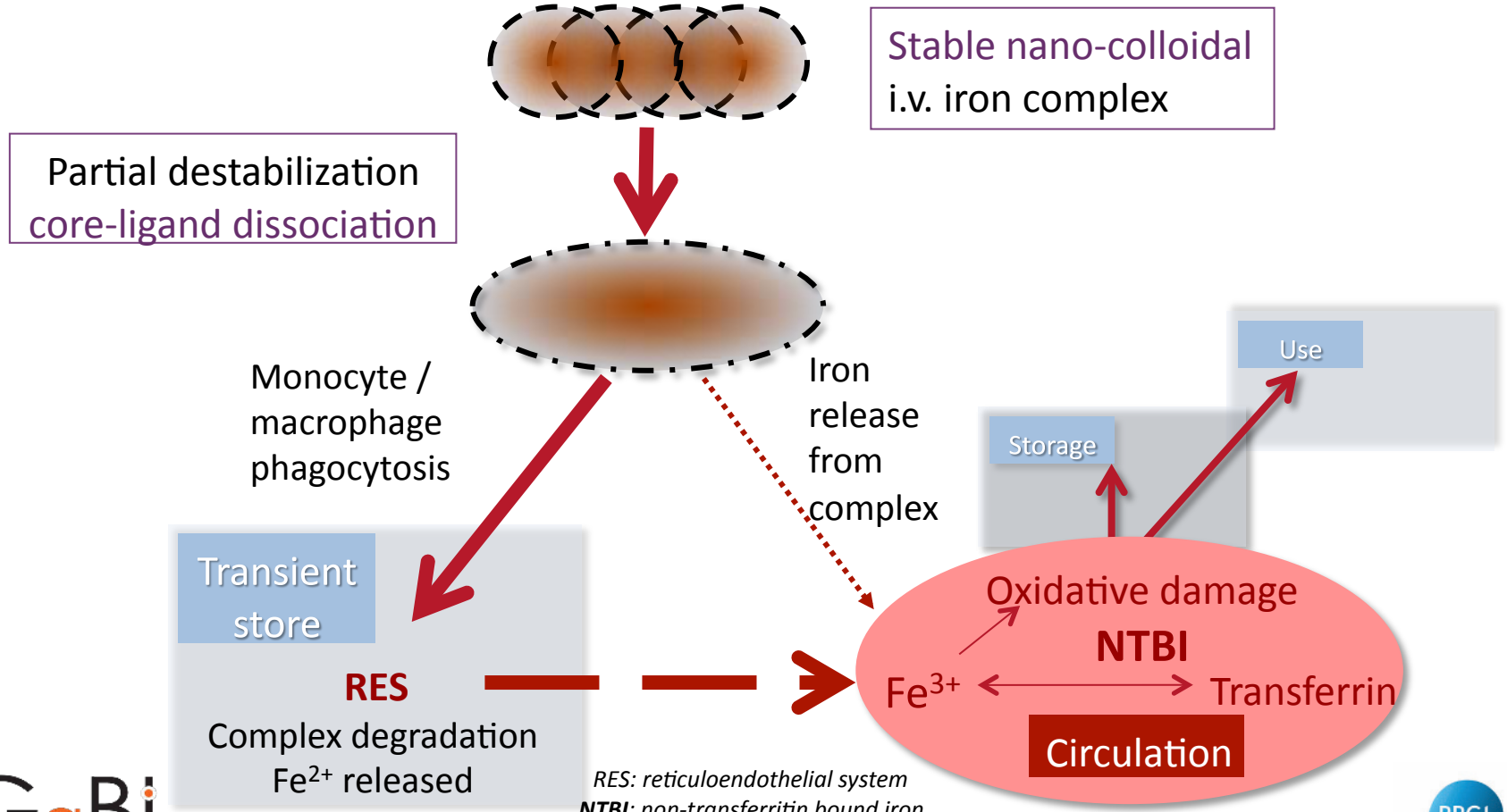
Release and Disposition of Iron in vivo



RES: reticuloendothelial system
***NTBI**: non-transferritin bound iron*

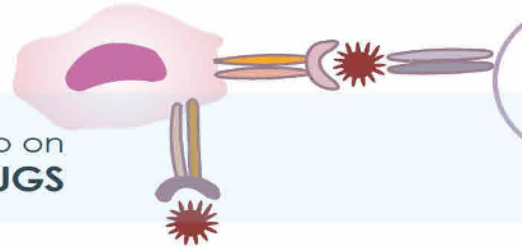
Therapeutic Equivalence (Comparability) of NBCD copies?

The generic paradigm is only applicable to fully characterized small molecules and not more valid for complex drugs

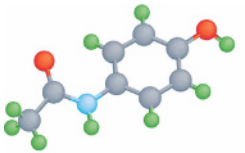
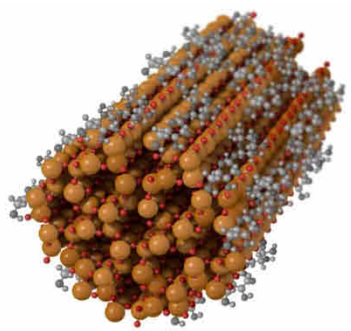
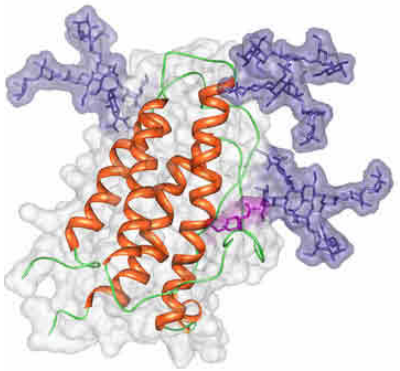
- **Conventional generic paradigm** (EMA, FDA):
- Pharmaceutical equivalence (identical API…)
- Bioequivalence in healthy subjects: comparable PK ($CI_{90\%}$ range 80-125%)
- Known mode of action

No clinical efficacy and safety studies required

Generics (interchangeable) No clinical testing needed



Approval of "Generic" Medicinal Products: There is Something missing

Generic paradigm	NBCD / Nanosimilars	Biosimilar approach
		
Small molecules drugs (m.w. <500) *e.g. ASA* **Fully characterized**	**Complex (non-biological) drugs** (m.range 43[IS]-150kDa) *e.g. polynuclear ferric hydroxide carbohydrate complexes* **Not fully characterized**	**Complex (biological) drugs** (m.range 5-150kDa) *e.g. EPO* **Not fully characterized**

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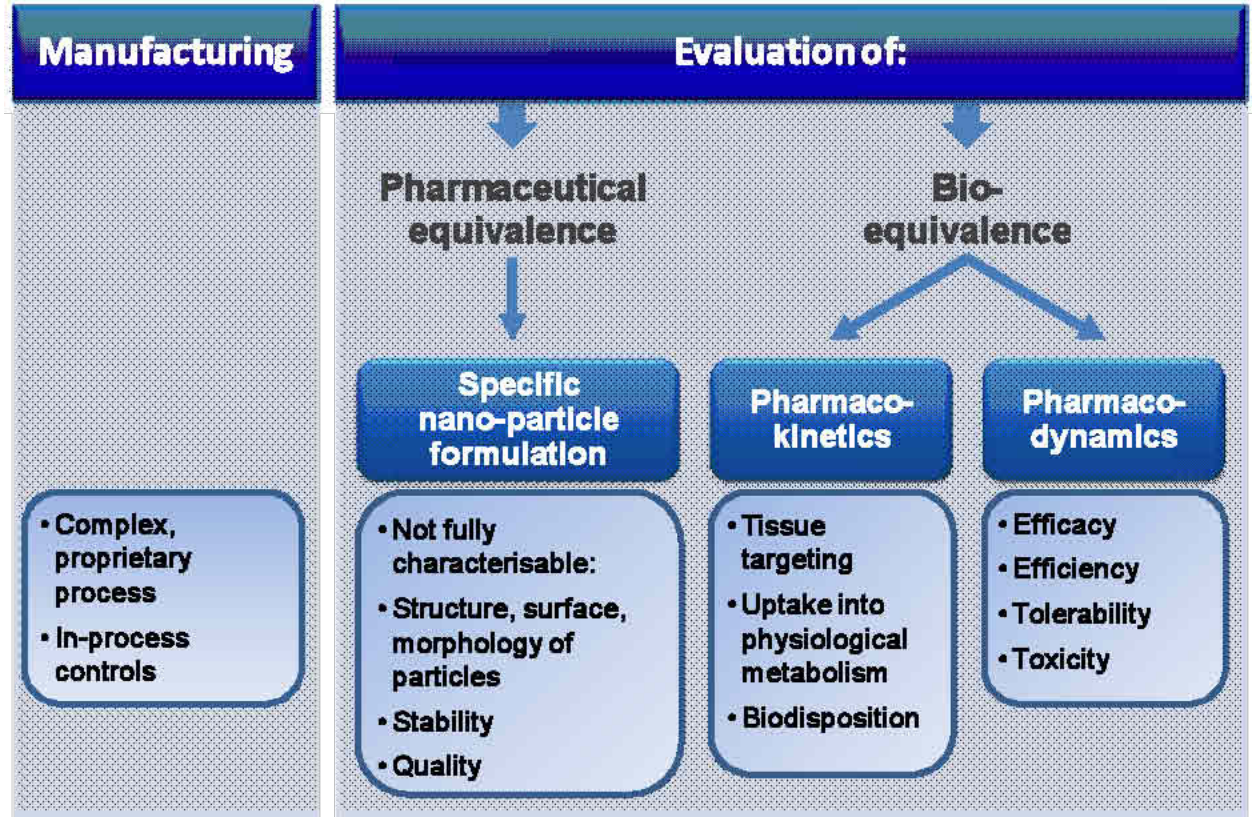
From Manufacturing to Efficacy and Safety (NBCD)



Mühlebach et al. in press GaBi 2013

Regulatory Challenge: How much Similar? Interchangeable / Substitutable (TE)

Authority Awareness for i.v. IS nanoparticle MP

EMA
(2011-2013)

2011

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

2013

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

2013

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

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

Draft

FDA
(2012)

This document is scheduled to be published in the Federal Register on 03/28/2012 and available online at http://federalregister.gov/a/2012-07456, and on FDsys.gov

4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2007-D-0369]

Draft Guidance for Industry on Bioequivalence Recommendations for Iron Sucrose Injection; Availability

AGENCY: Food and Drug Administration, HHS.

Dec 2012

Ferumoxytol injection

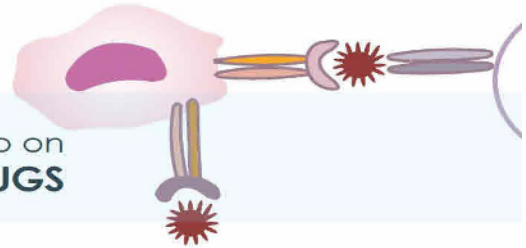
Apr 2013

TE evaluation IV iron gluconate (Ferrlicit vs. Nulecit)

GaBI Educational Workshops

First Asia Pacific Educational Workshop on
NON-BIOLOGICAL COMPLEX DRUGS

8 October 2013, Hilton Kuala Lumpur, Kuala Lumpur, Malaysia



The New Orleans Workshop Nov. 2010
Harmonization of Regulatory Approaches

Input: Scientific Evidence
Industry / Academia / Regulatory

Pharmaceutical Equivalence

In vitro / in vivo test performances?

Therapeutic equivalence and interchangeability of multisource (generic) drug products including complex drugs

Criteria, Approaches?

Bioequivalence

Output: Scientific Communication
Publications (global approach)

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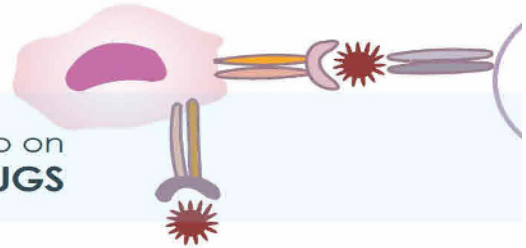


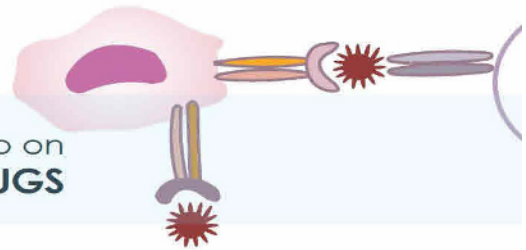
FDA: Sameness Approach

1. Equivalence of **sourcing**
2. Equivalence of **physico-chemical** properties (including purity)
3. Equivalence of **manufacture and product control**
4. Equivalence in biological and biochemical assays (**efficacy/safety profile**)
5. Equivalence of **in vivo** pharmacodynamic profile (therapeutic equivalent & **interchangeable**)

Pharmaceutical identity

Safety & therapeutic identity

Adapted from
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm220092.htm[.
Access 10.08.2010



EMA Reflection Paper: Non-clinical Studies of Iron Nanoparticles

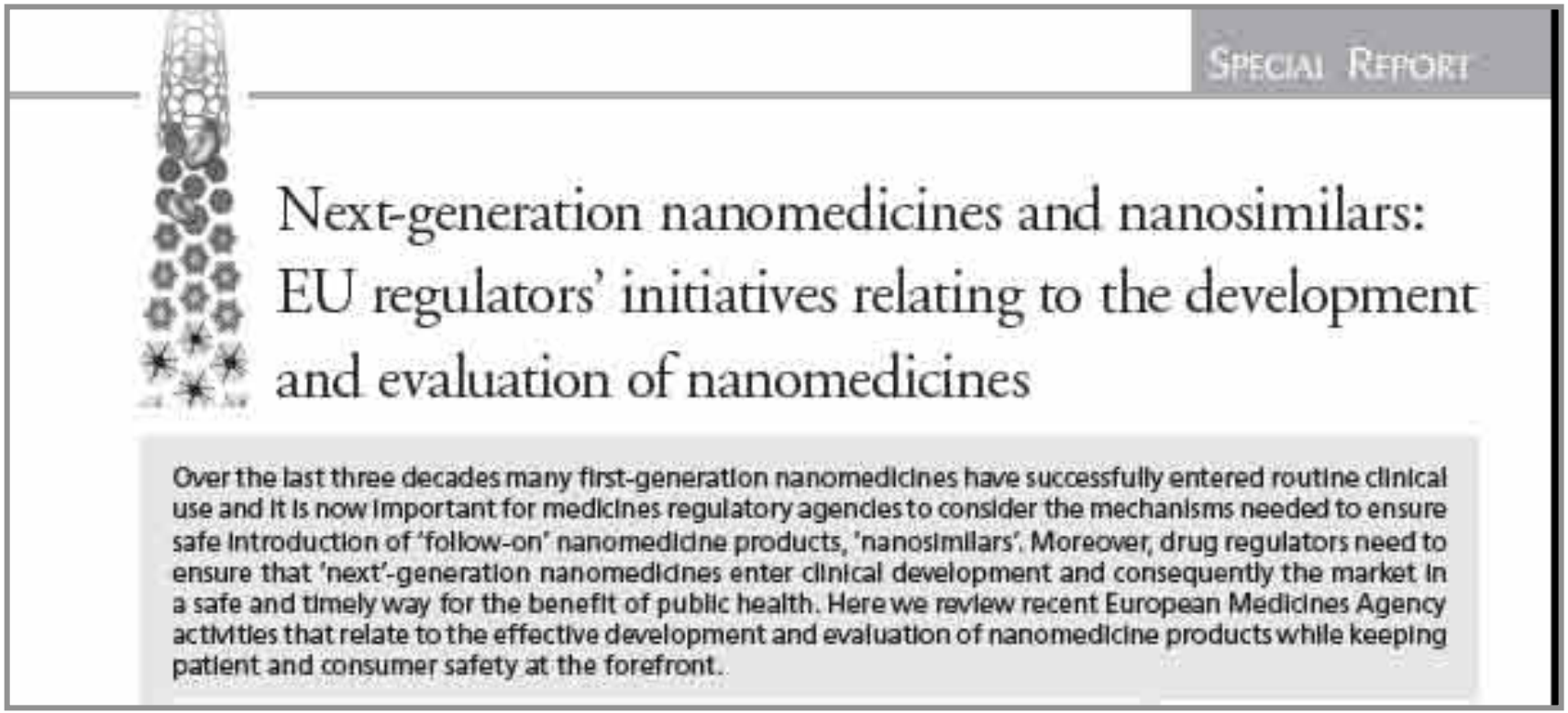
- The generic approach is generally not valid for approval of nanoparticle medicinal products
- At least three biological components need to be considered for comparative assessments of iron nanoparticles

Relevant compartments for the distribution of parenternal iron nanoparticles
1. Plasma
2. RES: macrophages e.g. spleen, lymph nodes, liver (Kupffer cells)
3. Target issues 3.2 Pharmacological target tissues e.g. bone marrow 3.2 Toxicological target tissues e.g. kidney, liver (hepatocytes), lung, heart

- For the comparison of iron nanoparticle medicinal products
  - time dependent plasma levels alone fail to detect relevant differences in the tissue distribution of iron
  - measurement of iron tissue distribution in humans may be not feasible
  - comparative data from non-clinical studies on the time-dependent iron content in the major target organs may be used to support the claim of essential similarity between iron nanoparticle medicinal products

C. Clarke Hospital Pharmacy Europe no 58 (Oct 2011): Roundtable Utrecht

NBCD follow-on MP: Nanosimilars



SPECIAL REPORT

Next-generation nanomedicines and nanosimilars: EU regulators' initiatives relating to the development and evaluation of nanomedicines

Over the last three decades many first-generation nanomedicines have successfully entered routine clinical use and it is now important for medicines regulatory agencies to consider the mechanisms needed to ensure safe introduction of 'follow-on' nanomedicine products, 'nanosimilars'. Moreover, drug regulators need to ensure that 'next'-generation nanomedicines enter clinical development and consequently the market in a safe and timely way for the benefit of public health. Here we review recent European Medicines Agency activities that relate to the effective development and evaluation of nanomedicine products while keeping patient and consumer safety at the forefront.

Nanomedicine 2013;8(5):849-856

RP: Data for Nano-Colloidal i.v. Iron Follow-on MP


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

- **Quality characterization is not sufficient** for assurance of the similarity
  - Extensive quality comparability to show high similarity
    labile Fe released, stability in plasma, size/variability iron core /Fe CH complex, hypersensitivity reactions, PK / body distribution, degradation products
  - Manufacturing: well defined and controlled
    material standards, impurities, intermediates, polymorphism of core, morphology of complex, particle size, stabilities, in vitro Fe release…
- **Weight of evidence approach**:
  quality, non-clinical & human PK studies
  validated analytical tools, PK, PD (markers) studies, relevant compartments
- **PV** RMS (chronic use, Fe tissue deposition, safety, oxidative stress…)

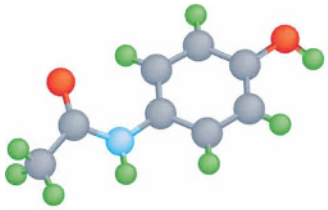
NBCD: Importance of Terms

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

*Since NBCD 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.*

G. Borchard, B. Flühmann, S. Mühlebach, RTP 2012;64:324-8

NBCD and Biologics: Similar but not the Same



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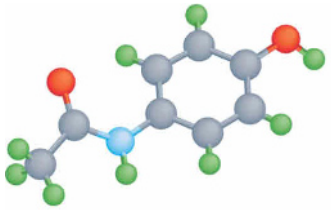
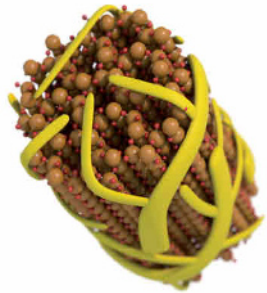


Small molecule

"Generic"
(identical copy)



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Complex molecules

"Similar"
(non identical copy)

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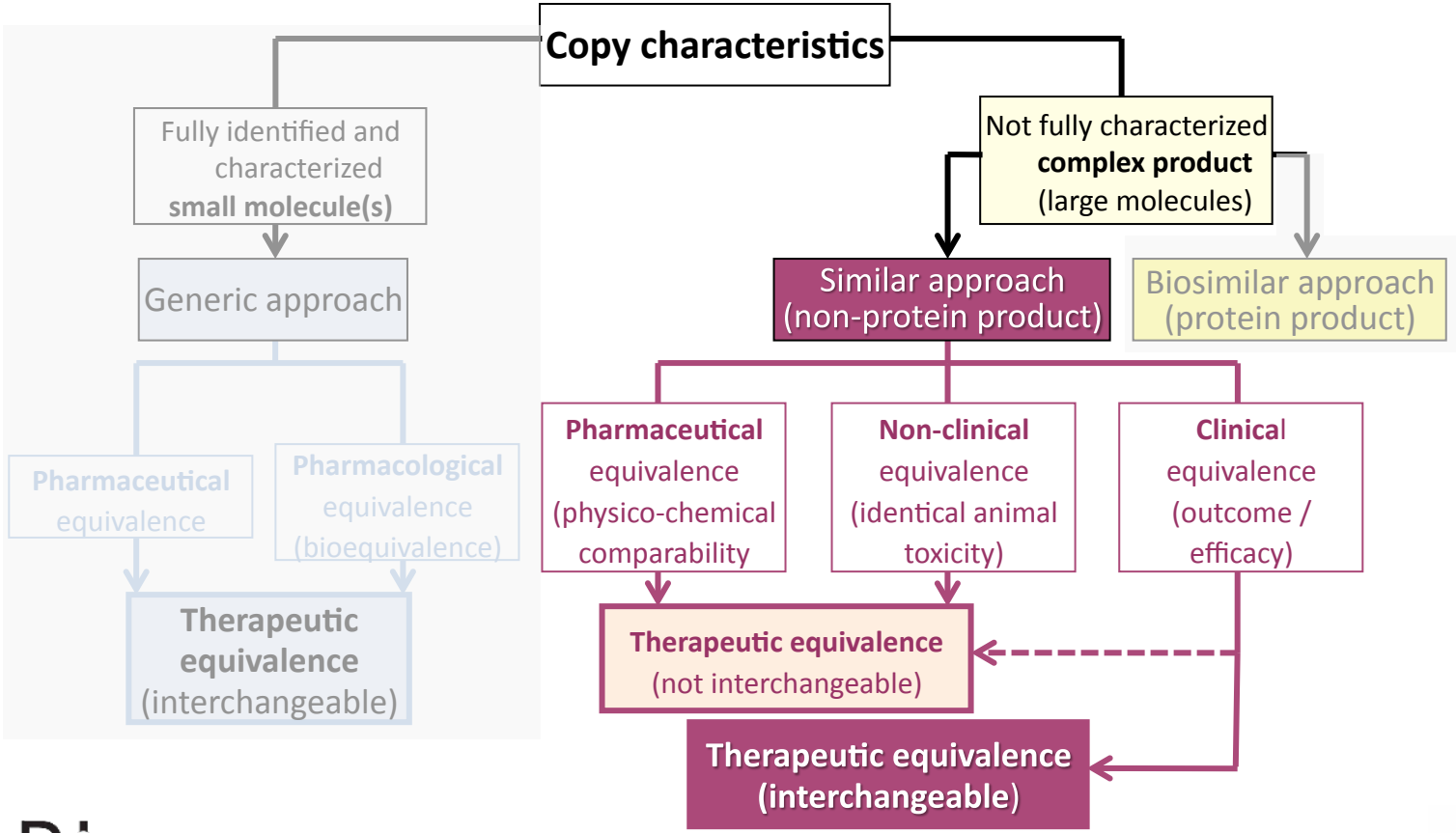
Schellekens et al. RTP 2011

Algorithm Proposal for Copy Authorizations



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Regul Toxicol Pharmacol 2011;59:176-183
AAPS-J online. How to regulate NBCD and their follow-on versions

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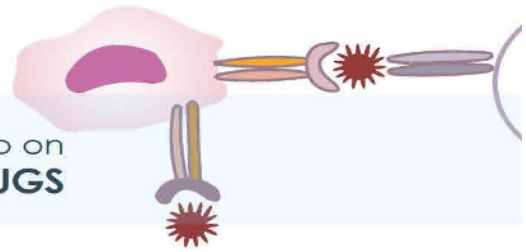

PV of NBCD Follow-on MP

- Once approved, proper pharmacovigilance standards must be established on brand name base (Risk Management Plan)
  - *Separate product codes must be established to track safety and efficacy for each product*

> "To help differentiate risk among the parenteral iron products (similar but not the same), the brand name of the product always has to be provided on medical records, death certificates, and adverse drug reaction reports"

Wysowski D. et al. Am. J. Hematol. 85:650–654, 2010

Upcoming NYAS Event