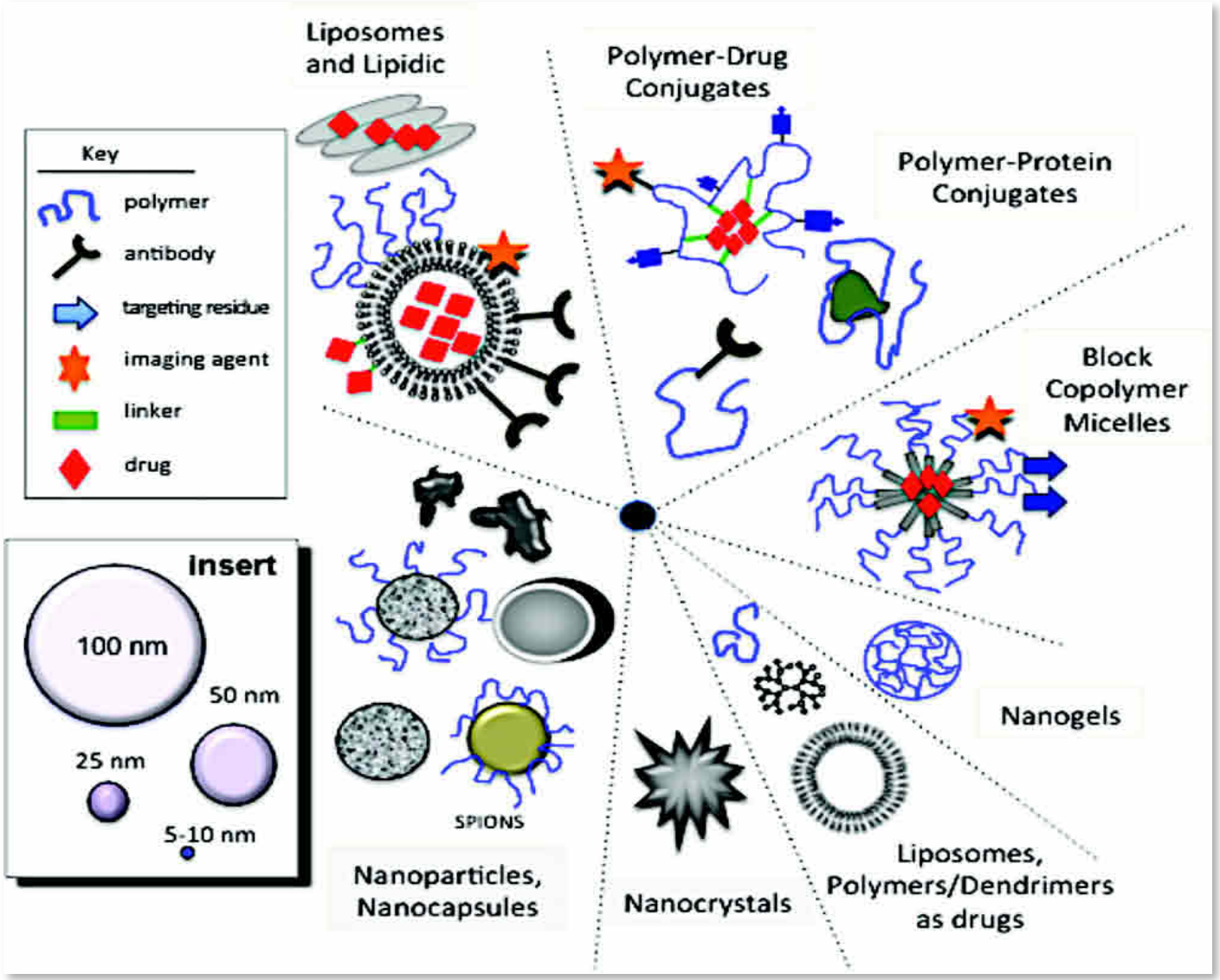
Professor Gerrit Borchard, PharmD, PhD, Switzerland

- Professor of Biopharmaceutical Sciences
- President, Swiss Society of Pharmaceutical Sciences
- Vice President, European Federation of Pharmaceutical Sciences (EUFEPS)
- School of Pharmaceutical Sciences
- University of Geneva, University of Lausanne

Measuring complexity – characterization of non-biological complex drug and regulatory consequences

Professor Gerrit Borchard, PharmD, PhD
8 October 2013

Nanomedicines

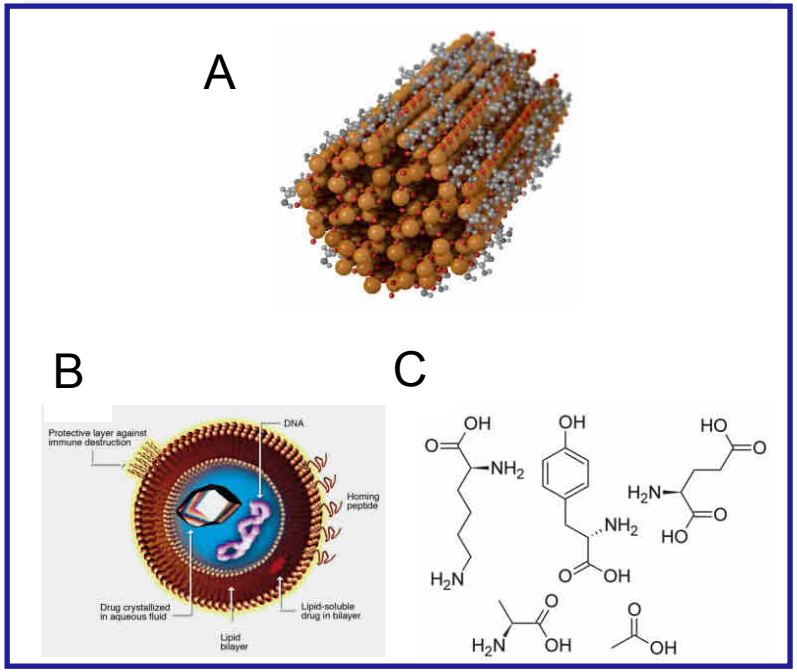


Duncan & Gaspar; Mol Pharmaceutics, 2011

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

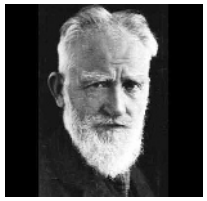
Adapted from poster PHC030
17th EAHP conference 2011



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

Where worlds meet: Bio-Pharmaceutics

- One determinant for the fate of nanomedicines is the interaction of the biological environment with their surface.
- Surface modification of nanoparticles leads to change in PK, PD, toxicity, organ deposition, immunogenicity,…
- Paradigm changes due to deeper understanding of biology.

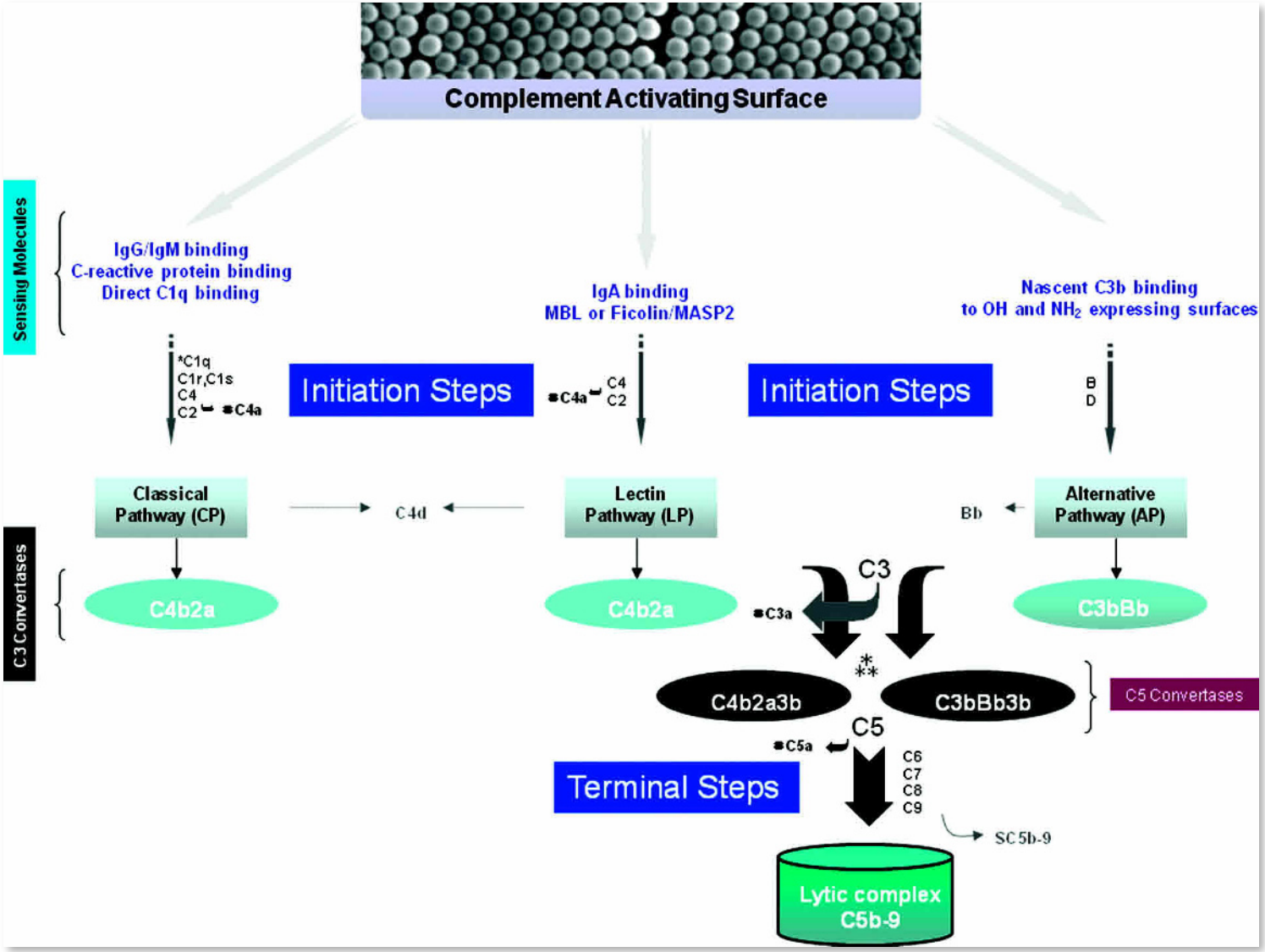


Opsonization

"Opsonin is what you butter the disease germs with to make your white blood corpuscles eat them."

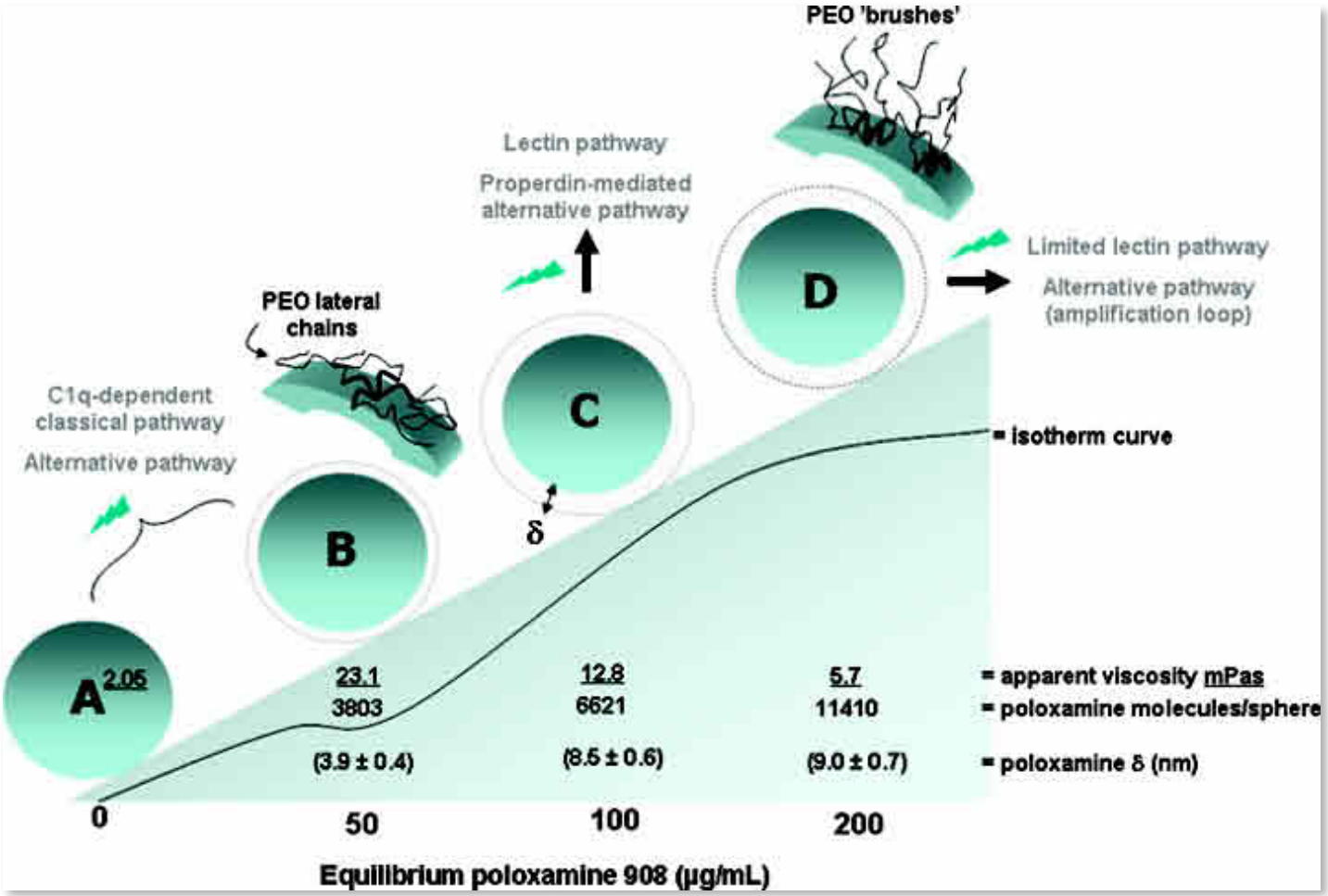
George Bernard Shaw, The Doctor's Dilemma

Surface Modification – Pathway Switching



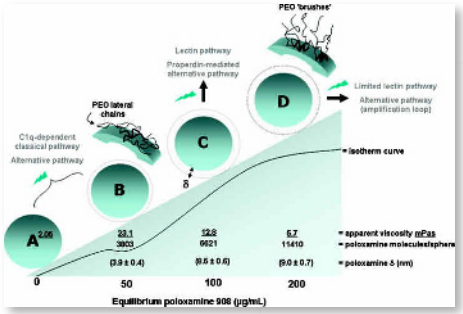
Hamadet al., ACS Nano, 2010

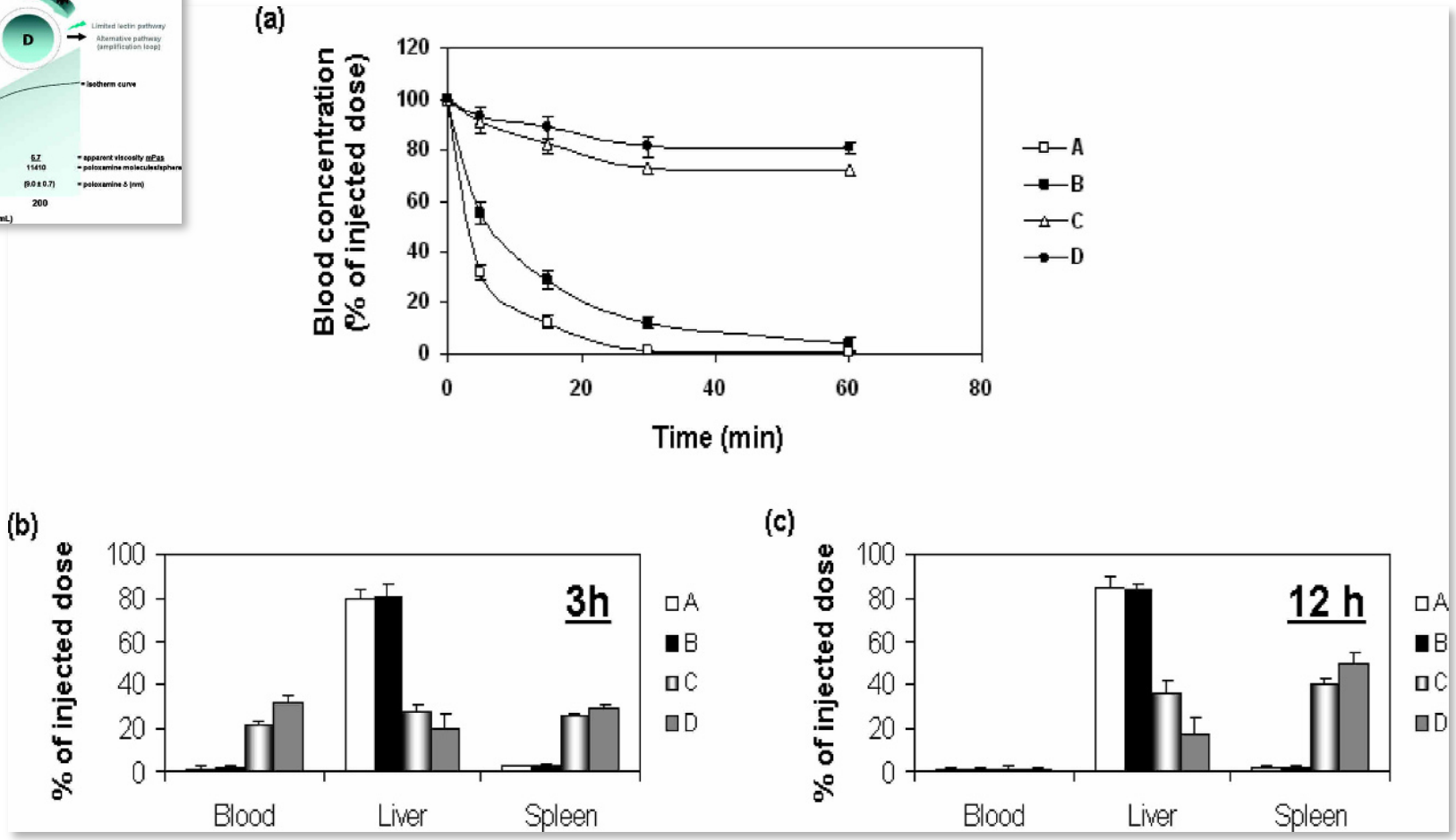
Surface Modification – Pathway Switching



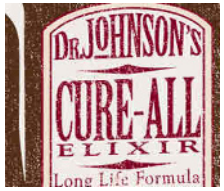
Hamadet al., ACS Nano, 2010

Surface Modification – Pathway Switching





Hamadet al., ACS Nano, 2010

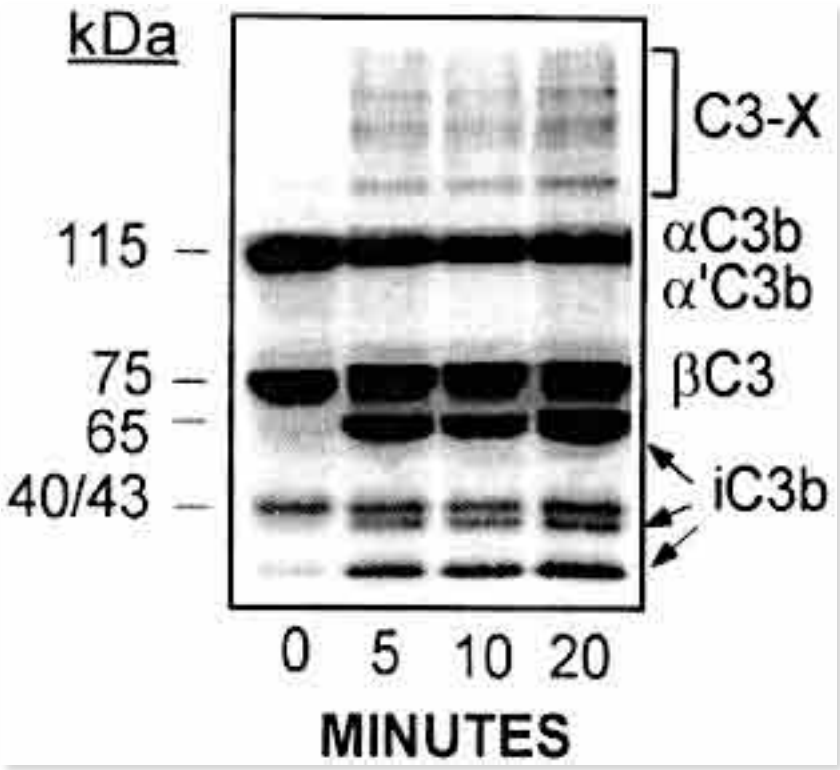


PEGylation

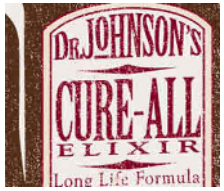
- Covalent binding of polyethylene glycol (PEG) to complex drugs (= PEGylation) to confer “stealth effect”.
- Ninjasomes, stealth liposomes, etc.
- Accelerated blood clearance (ABC): increased clearance upon re-injection of PEGylated liposomes, in rats, mice and Rhesus monkeys (Ichihara et al., Pharmaceutics, 2011).
- Activation of complement system on re-injection, development of T cell independent anti-PEG IgM.

PEGylation Activates Complement

Complement activation in human serum containing ^{125}I-labelled C3 by Doxil®.



Szebeni et al., J Liposome Res, 2000



PEGylation Activates Complement…or does it?

Pharmaceutical Research
July 2013, Volume 30, Issue 7, pp 1729-1734

The Immunogenicity of Polyethylene Glycol: Facts and Fiction

Huub Schellekens, Wim E. Hennink, Vera Brinks

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ABSTRACT

An increasing number of pegylated therapeutic proteins and drug targeting compounds are being introduced in the clinic. Pegylation is intended to increase circulation time and to reduce an immunogenic response. Recently however a number of publications have appeared claiming that the polyethylene glycol (PEG) moiety of these products in itself may be immunogenic and that the induced anti-PEG antibodies are linked to enhanced blood clearance and reduced efficacy of the products. A critical review of the literature shows that most, if not all assays for anti-PEG antibodies are flawed and lack specificity. Also the biological effects induced by anti-PEG antibodies lack the characteristics of a *bona fide* antibody reaction. Standardization of the anti-PEG assays and the development of reference sera are urgently needed.

Characterization PECs

- Size
- Scanning electron microscopy
- Lyophilization
- Electrophoretic mobility
- Stability in physiological media
- *In vitro* assays

The EDQM and the European Pharmacopoeia

Gerrit Borchard, Université de Genève

Susanne Keitel, EDQM

The Pharmacopoeia in the EU Legislation

- The Ph. Eur. is legally binding.
- Legislation foresees a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market.
- An excellent tool to ensure that monographs are not cast in stone but routinely updated to reflect the state-of-the-art.

Working group

- Prof. Gerrit Borchard, University of Geneva (Head)
- Prof. Heike Bunjes, University of Braunschweig
- Dr. Lino Liverani, Opocrin SpA, Modena
- Dr. Kim Nordfjeld, Pharmacosmos A.S., Holbaek
- Dr. Erik Philipp, Vifor Int. Ltd., St. Gallen
- Dr. Maria Rosa Virto Garcia, AEMPS, Madrid

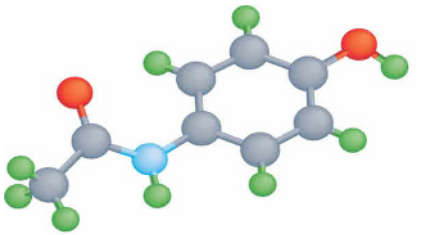
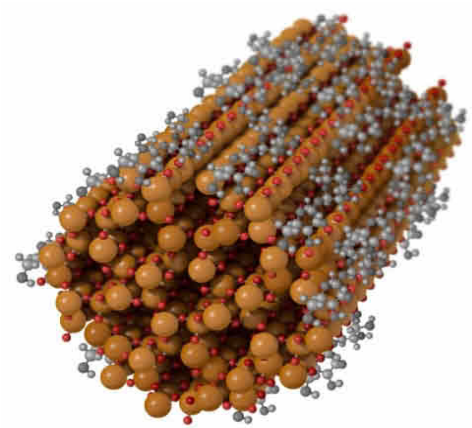
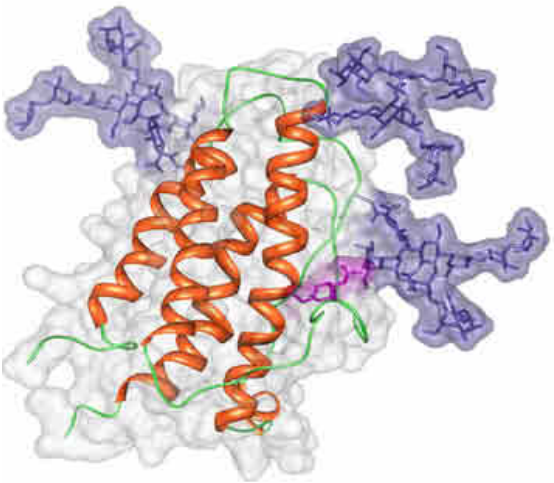
Therapeutic equivalence (comparability) of copies

Conventional generic paradigm (EMA, FDA):

- Pharmaceutical equivalence (identical API/formulation): **the same**
- Bioequivalent in healthy subjects: **comparable in volunteers** comparable PK (80-125% range [CI_{90}])
- Generic drugs: **interchangeable/substitutable**
- No clinical efficacy and safety studies required
- The generic paradigm is only applicable to fully characterized active pharmaceutical ingredients (small molecules)

Schellekens et al., Regul Toxicol Pharmacol, 2011

“Generic” medicinal product approval: There is something missing

Generic paradigm	?	Biosimilar approach
		
Small molecules (m.w. <500) Fully characterized	Complex (non-biological) drugs (m.w. range 43[IS]-150kDa) Not fully characterized	Complex (biological) drugs (m.w. range 5-150kDa) Not fully characterized

Schellekens et al., Regul Toxicol Pharmacol, 2011

Example: liposomal doxorubicin

FDA Draft guidance (2010) recommends two studies to demonstrate bioequivalence

Clinical:

- single-dose, two-way cross-over, liposomal and free doxorubicin
- Bioequivalence (90% CI) based on AUC and C_{max} for liposomal and free doxorubicin

In vitro:

- Liposome size distribution (D_{10}, D_{50}, D_{90})
- Bioequivalence (90% CI) based D_{50} and SPAN $(D_{90}-D_{10})/D_{50}$ or PDI

Guidance on:

- Same drug product composition (lipids, distribution of molecular species)
- Active liposome loading process (ammonium sulfate gradient, QbD driven)
- Equivalent liposome characteristics

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf

Example: liposomal doxorubicin

Equivalent liposome characteristics:

- *In vitro* characterization in at least three batches of abbreviated new drug application (ANDA) and reference listed drug (RLD), with at least one ANDA batch produced by commercial scale process
- Liposome composition: lipid content, drug content (free & encapsulated), concentration of internal and total sulfate, ammonium, histidine and sucrose
- State of encapsulated doxorubicin (precipitate in RLD)
- Internal environment: volume, pH, sulfate and ammonium concentrations
- Liposome morphology and number of lamellae
- Lipid bilayer phase transitions
- Liposome size distribution
- Grafted PEG layer thickness
- Electrical surface potential or charge
- In vitro leakage under multiple physiological conditions

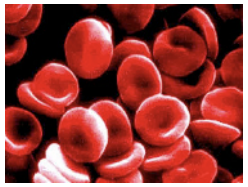
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf

Example: liposomal doxorubicin

Examples of in vitro leakage conditions of doxorubicin liposomes

In Vitro Drug Leakage Condition	Purpose	Rationale
At 37°C in 50% human plasma for 24 hours	Evaluate liposome stability in blood circulation.	Plasma mostly mimics blood conditions.
At 37°C with pH values 5.5, 6.5, and 7.5 for 24 hours in buffer	Mimic drug release in normal tissues, around cancer cells, or inside cancer cells	Normal tissues: pH 7.3 Cancer tissues: pH 6.6 Insider cancer cells (endosomes and lysosomes): pH 5-6 (Endosome and lysosomes of cancer cells may be involved in liposome uptake and induce drug release).
At a range of temperatures (43°C, 47°C, 52°C, 57°C) in pH 6.5 buffer for up to 12 hours or until complete release	Evaluate the lipid bilayer integrity	The phase transition temperature (Tm) of lipids is determined by lipid bilayer properties such as rigidity, stiffness and chemical composition. Differences in release as a function of temperature (below or above Tm) will reflect small differences in lipid properties
At 37°C under low-frequency (20 kHz) ultrasound for 2 hours or until complete release.	Evaluate the state of encapsulated drug in the liposome.	Low-frequency ultrasound (20 kHz) disrupts the lipid bilayer via a transient introduction of pore-like defects and will render the release of doxorubicin controlled by the dissolution of the gel inside the liposome.

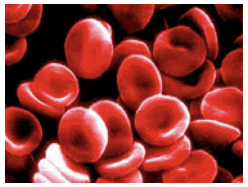
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf



Iron-carbohydrate drugs

- Colloidal formulations of polynuclear iron(III)-oxyhydroxide stabilized by a complex coating of carbohydrates.
- Iron core is taken up by RES, acting as short-term storage.
- Release from RES and utilization in erythropoiesis.
- Therapy of iron deficiency anemia in chronic kidney disease, pregnancy, malabsorption, etc.

Stein et al., Nature Rev Gastroenterol Hepatol, 2010
Kudasheva et al., J Inorg Biochem, 2004



Iron-carbohydrate drugs

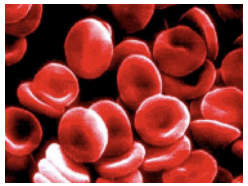
FDA Draft guidance on Iron Sucrose (2012) recommends 2 studies to demonstrate bioequivalence

Clinical:

- single-dose, randomized, parallel
- Bioequivalence (90% CI) based on baseline-corrected total iron and transferrin-bound iron
- Analytes to be measured:
  - baseline adjusted total iron in serum
  - baseline adjusted transferrin-bound iron (TBI) in serum

In vitro:

- Particle morphology by atomic force microscopy (AFM) including a placebo product
- Particle diameter by dynamic light scattering D_{10}, D_{50}, D_{90} and SPAN $(D_{90}-D_{10})/D_{50}$



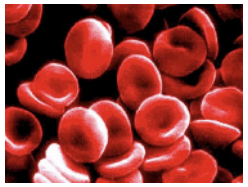
Iron-carbohydrate drugs

Comments to FDA Draft guidance on Iron Sucrose:

Subtle variations in the production process may lead to changes in:

- Structure of iron core
- Size, size distribution, complex molecular weight distribution
- Sucrose-to-iron ratio affecting stability and iron release
- ADME-T profile

Due to body disposition pattern of Iron Sucrose in the reticuloendothelial system (RES), sampling in serum is **insufficient** to determine bioequivalence.



Iron-carbohydrate drugs

Comments to FDA Draft guidance on Iron Sucrose:

- Committee for Medicinal Products for Human Use (CHMP) of EMA suggested non-clinical comparability studies including assessment of iron distribution in at least plasma, RES and target tissues in suitable animal models.

- The “Leiden proposal” of the Joint working Party on NBCD demanded at least comparison of safety in rodents, once pharmaceutical quality is assured (Schellekens et al., Regulat Toxicol Pharmacol, 2011).

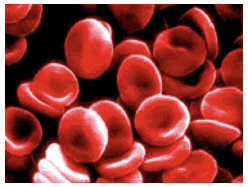
- If studies show lack of induction of oxidative stress: Therapeutic equivalence.

- Interchangeability: clinical studies necessary.

FDA scrutiny for in vivo PK equivalence (Apr '13)

Therapeutic equivalence evaluation of Nulecit™ vs. Ferrlecit™ in a 3-years project

- Non-transferrin bound iron (NTBI) formation and comparison in vivo: oxidative stress, inflammation?
- Physicochemical characterization incl. labile iron
- In vivo uptake labile iron leakage compared to RLD
- Phagocytosis assay (RES uptake)
- Prospective, well-controlled studies on iron distribution in tissue (preclinical species)
- Compare NTBI levels in hemodialysis patients (cross-over)



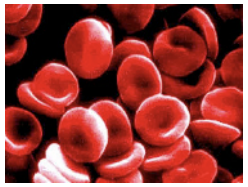
Iron-carbohydrate drugs

Draft:

"Reflection paper o… …ements for intravenous ir… …colloidal products deve… …nce to an innovator …dicinal product"

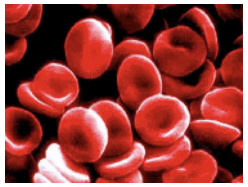
Start of consultation: 15/9/2013, end: 28/2/2014

EMA/CHMP/SWP/620008/2012



Iron-carbohydrate drugs

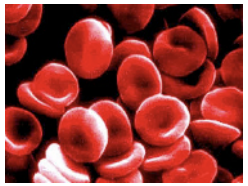
"…current scientific knowledge and regulatory experience for characterisation of **nano-sized colloidal preparations** indicate that quality characterisation on its own, would not provide sufficient assurance of the **similarity** between the two products, even if the quality tests performed show similarity. …data from quality, non-clinical and human pharmacokinetic studies is **required**."



Iron-carbohydrate drugs

"…Reflection paper should be read in connection with guidelines (among others):

- ICH Q5E section 1.4 Note for Guidance on Biotechnological/biological Products
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (Draft EMA/CHMP/BWP/247713/2012)"



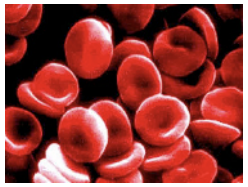
Iron-carbohydrate drugs

- ## Quality characterisation of test product:

  Particle size/distribution, surface charge, specific surface area, structure/composition of carbohydrate, identification and control of intermediates in manufacturing process, labile iron, polymorphic forms, impurities (di/trivalent iron), microscopic morphology, in vitro release in clinically relevant media, degradation path, storage/in-use stability,…

- ## Bio-distribution studies:

  Relevant compartments: plasma (serum), red blood cells, RES (macrophages in spleen, liver), pharmacological (bone marrow) and toxicological (kidney, hepatocytes, lung, heart) target tissues



Iron-carbohydrate drugs

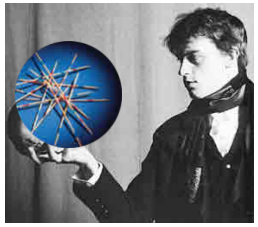
- Clinical:
  - Pharmacokinetic studies
  - Efficacy and Safety studies
- Post-marketing:
  - Pharmacovigilance
  - Risk Management Plan (RMP)

Conclusions

- Validated, well-designed, comparative clinical studies are needed, in addition to pre-clinical studies, to document therapeutic equivalence of NBCD originator products and intended copies.

- Only if clinical data provide sufficient proof of therapeutic equivalence, the two products may be considered interchangeable.

- Post-approval pharmacovigilance is essential.



Conclusion

There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy.

William Shakespeare, Hamlet