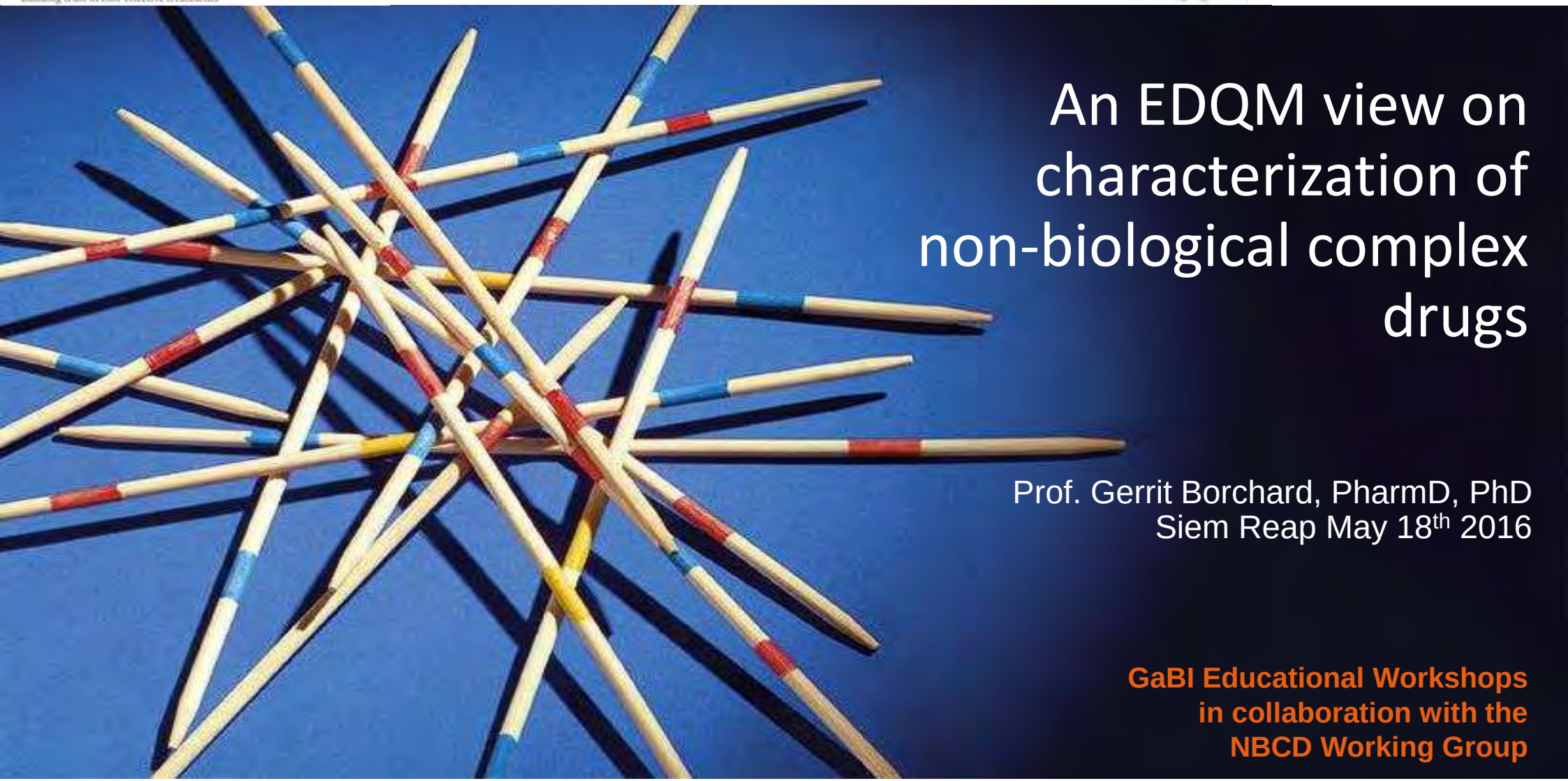
GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

PPCI
Pro Pharma Communications International

Non Biological Complex Drugs working group

lygature



An EDQM view on characterization of non-biological complex drugs

Prof. Gerrit Borchard, PharmD, PhD
Siem Reap May 18th 2016

GaBI Educational Workshops in collaboration with the NBCD Working Group

European Directorate for the Quality of Medicines & HealthCare (EDQM)

- A Council of Europe Directorate, based on the Convention on the Elaboration of a *European Pharmacopoeia* (PA, 1964)

  - Mission: to contribute to a basic human right: access to good quality medicines and healthcare

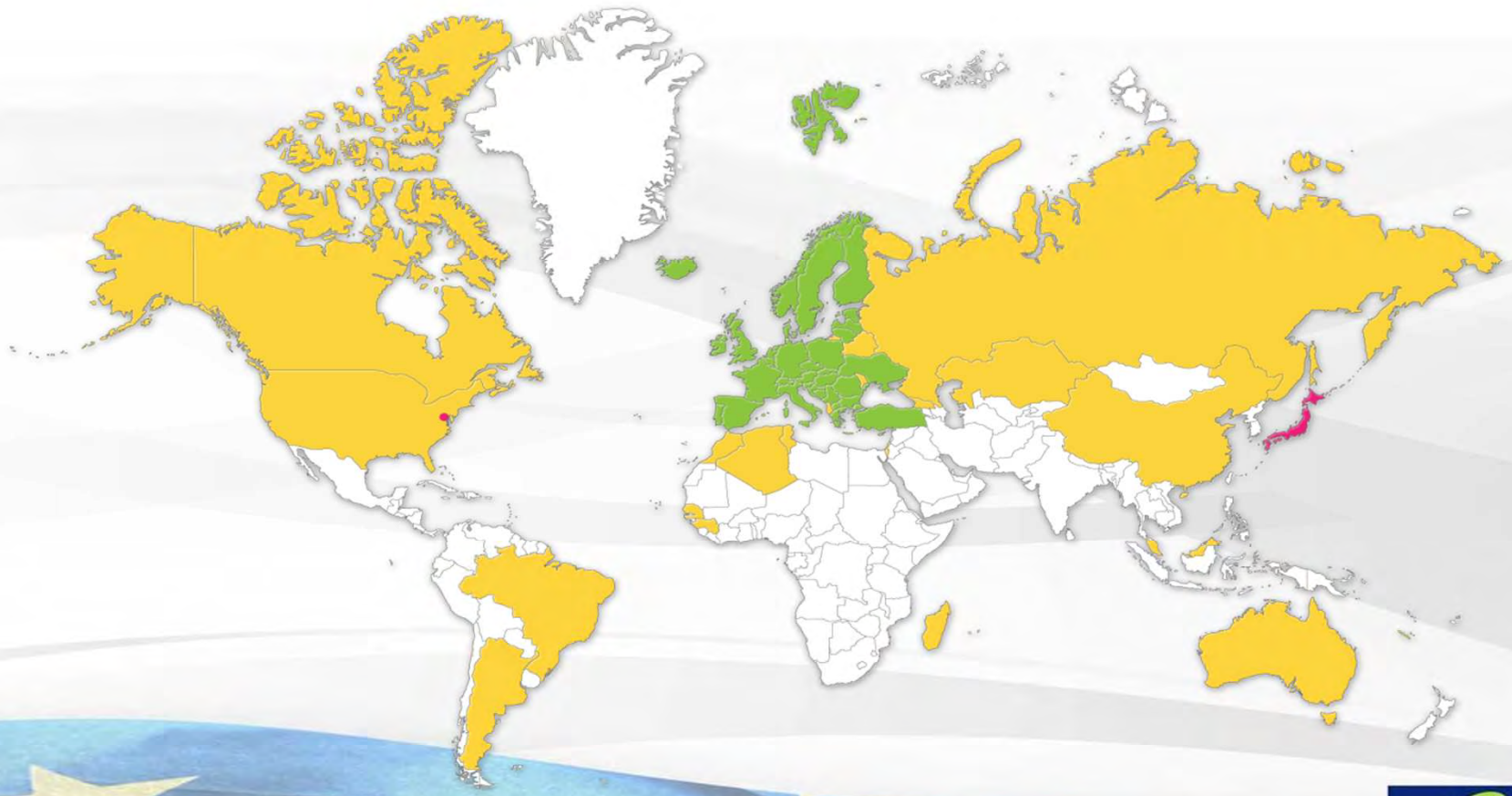
European Pharmacopoeia (Ph. Eur.)

- Protecting public health - one common compulsory standard
- The Ph. Eur. is the **official pharmacopoeia** in Europe – complemented by national pharmacopoeias for texts of interest to only one Member State
- **Mandatory** at the same date in 37 Member States (CoE) and the EU (decision of Ph. Eur. Commission).
- Legally binding **quality standards** for ALL medicinal products, i.e. raw material, preparations, dosage forms, containers,...

Ph. Eur. Commission

- One delegation per member state or observer
- 37 Member States plus a delegation from the EU (a representative from DG Health & Consumer and the EMA);
- 23 observer countries and World Health Organization (WHO).
- Delegates from health ministries, health authorities, pharmacopoeias, universities, industry appointed by national authorities on basis of expertise.
- Three sessions a year; texts are adopted by **unanimous** vote.
- Currently 20 permanent Groups of Experts & 52 ad-hoc Working Parties -> 250 meeting days/year
- Composition of groups of experts decided by Ph. Eur. Commission
- One Secretariat: EDQM

Ph. Eur. Members and Observers



edqm European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

The Pharmacopoeia in the EU Legislation

"The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it.

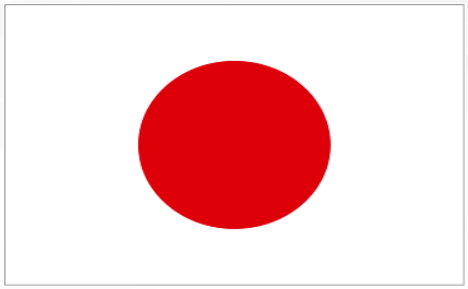
In respect of other substances, each Member State may require observance of its own national pharmacopoeia…"

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.

Pharmacopoeial Harmonisation

Three major pharmacopoeias



Japanese Pharmacopeia

Governmental

Ph. Eur.

EDQM, Council of Europe

Inter-governmental

US Pharmacopoeia

Independent of Government

The PDG & Harmonisation

- Pharmacopoeial Discussion Group (PDG), set up in 1990
- Drives international harmonisation of pharmacopoeial requirements among the Ph. Eur., JP and USP - a single set of global specifications.
- Aims:
  - Avoid redundant testing by suppliers and pharmaceutical industry to meet different standards
  - Reduce the overall cost of pharmaceutical research world-wide by avoiding duplication of work (preparation of dossiers and studies)
  - Reduce the time required for medicines to be made available to patients

Pharmacopoeial Harmonisation

- Monographs and general methods of analysis proposed by national associations of manufacturers of pharmaceutical products
- To ensure rapid publication of signed-off texts, the PDG procedure has been integrated into the Ph. Eur. procedure
- Texts are published in Pharmeuropa and approved by the Ph. Eur. Commission
- Harmonisation in parallel and in coordination with ICH activities
- Priority of pharmacopoeias according to EU legislation
  Ph. Eur. > national pharmacopoeia > third country pharmacopoeias, e.g., USP, JP

Non-Biological Complexes (NBC) Working Party

- Created in June 2011 based on an initiative by SwissMedic and following the decision of the Ph. Eur. Commission to add on its work programme the elaboration of a monograph on ***Iron sucrose concentrated solution***.
- Elaboration of monographs on **non-biological complexes** (e.g., nanoparticle solutions, like for example iron sucrose concentrated solution) allocated to the group by the Commission.

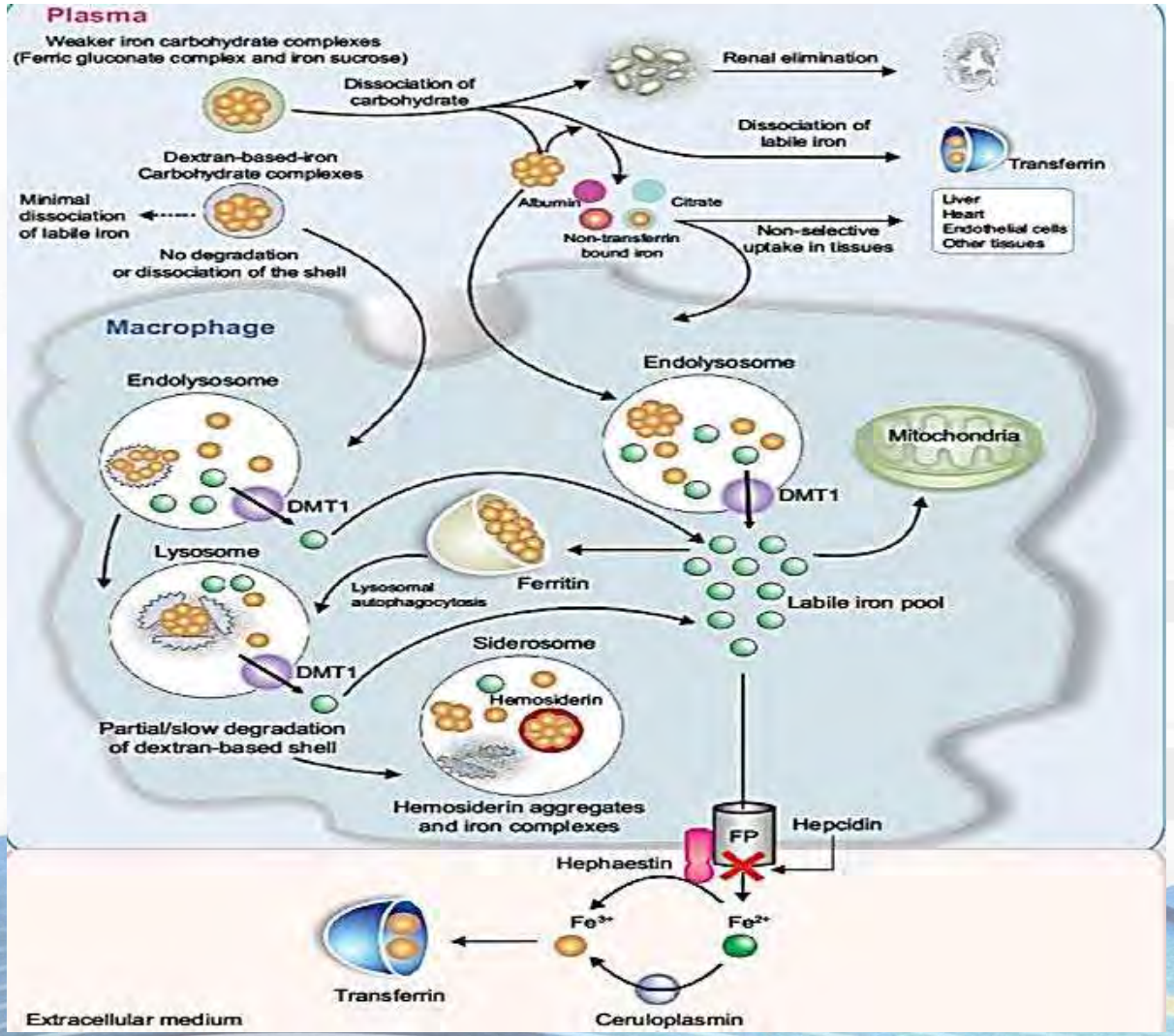
Working group

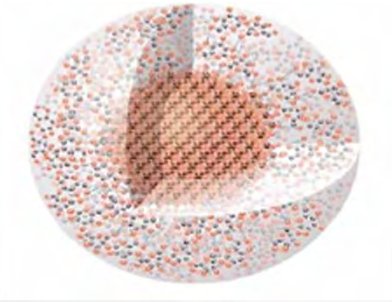
- Prof. Gerrit Borchard, University of Geneva (CH, chair)
- Prof. Heike Bunjes, University of Braunschweig (D)
- Dr. Lino Liverani, Opocrin SpA, Modena (I)
- Dr. Kim Nordfjeld, Pharmacosmos A.S., Holbaek (DK)
- Dr. Erik Philipp, Vifor Int. Ltd., St. Gallen (CH)
- Dr. Fiona Roos, Cilag, Schaffhausen (CH)
- Dr. Maria Rosa Virto Garcia, AEMPS, Madrid (E)
- Dr. René Thürmer, BfArM, Bonn (D)

Iron sucrose injection in BP, USP, and Ph. Eur. draft

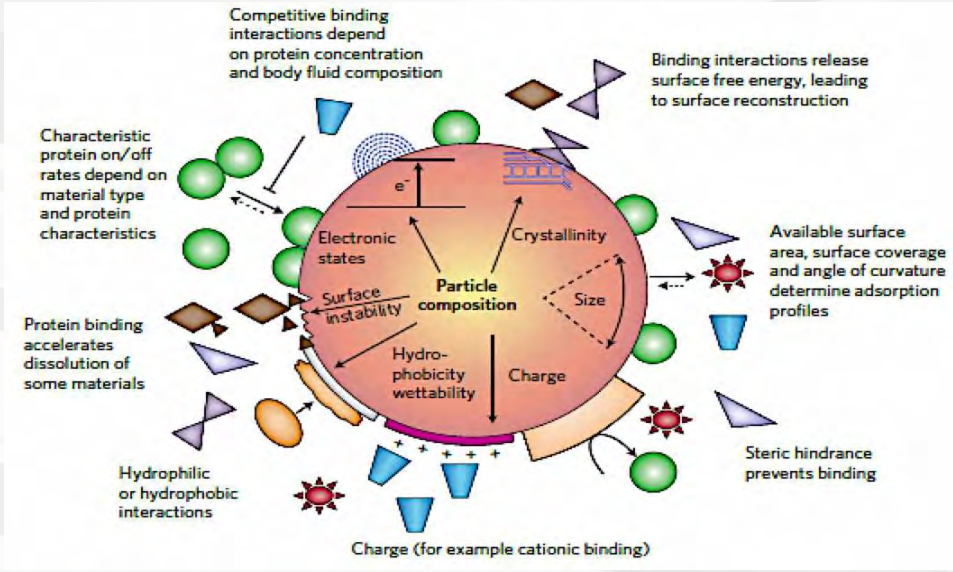
USP	BP	Ph. Eur. draft
"Iron Sucrose Injection is a **sterile**, colloidal solution of ferric hydroxide in complex with Sucrose in water for Injection. It contains no less than 95.0 percent and not more than 105.0 percent of the labeled amount of iron. Sodium Hydoxide may be added to adjust the pH. It contains no anti-microbial agent, chelating agent, dextran, gluconate, or other added substances."	"Iron Sucrose is a **sterile** colloidal solution containing a complex of iron(III)hydroxide with sucrose of average molecular weight between 34000 and 60000."	"Iron Sucrose Concentrated Solution is a colloidal solution containing a complex of iron(III) hydroxide with sucrose of weight average relative molecular weight (Mw) between 34000 and 60000 Da" "Content: Iron: 95.0 to 105.0 per cent of the labeled amount of iron. Sucrose/Iron ratio (w/w) of 13:1 to 17:1."
Identification of iron, sucrose and M_W	Identification of Iron, Sucrose and M_W	Identification of Iron, Sucrose and M_W
Tests: Alkalinity, Osmolality, Clarity, M_W (34-60 kDa and M_N (>24 kDa) by SEC, Quantification of Iron and Sucrose.	Tests: Specific gravity, Bacterial Endotoxins, Alkalinity, pH, Osmolarity, Absence of LMW Fe(II) and Fe(III) complexes, Turbidity, Particulate matter, Fe(II), Chloride content, Quantification of Sucrose and Iron	Tests: pH, Alkalinity, **Labile Iron**, Chloride, **Particle size** (distribution), Molecular weight (distribution), **Zetapotential**, Quantification of Iron and Sucrose, Related substances, Chemical structure of iron core (?)

Opsonisation: phagocytosis of i.v. iron carbohydrate nanoparticles



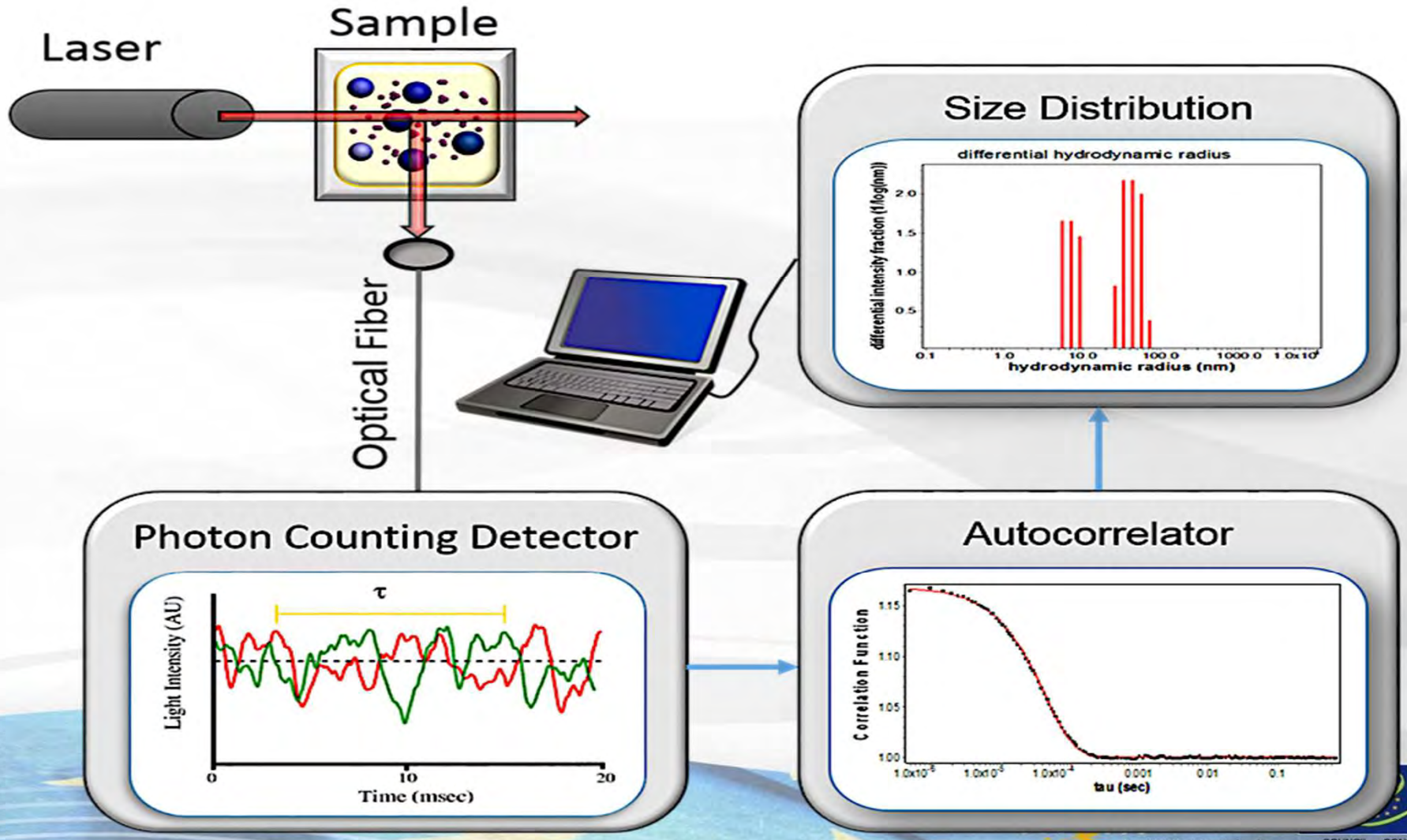


Iron sucrose
Venofer®



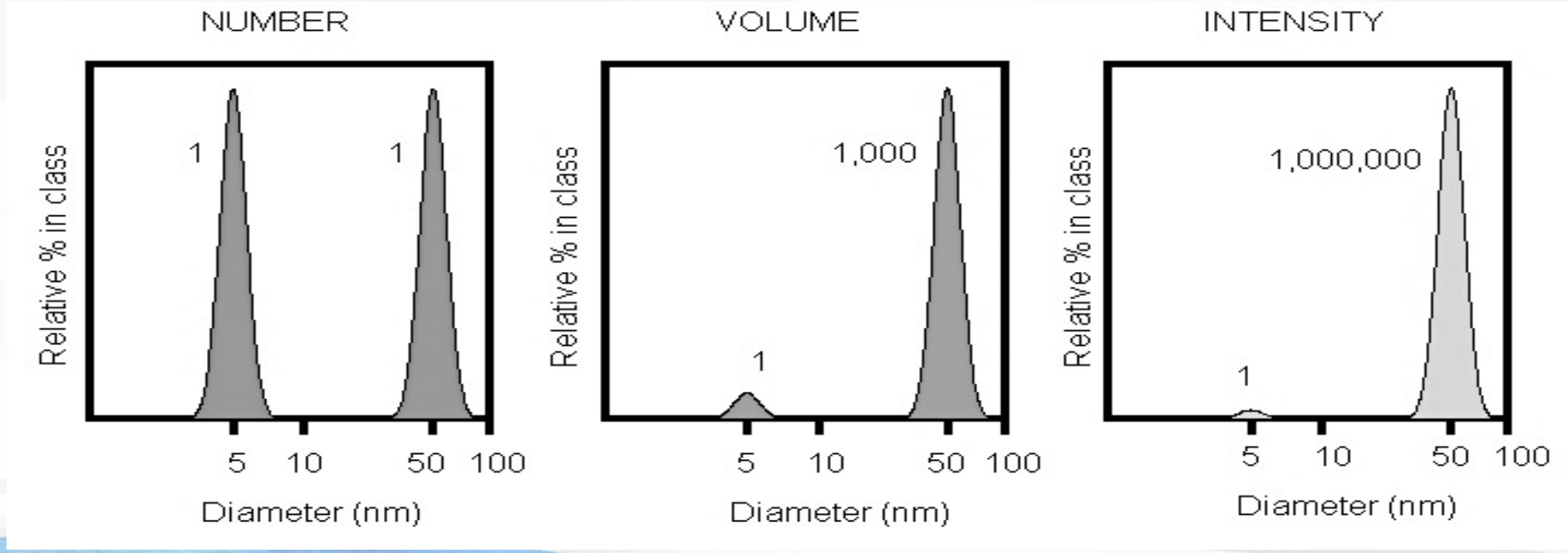
Nel et al., Nat. Mater. 8, 543-57, 2009.
Drug Design, Dev Therap 8, 2475-91, 2014.

Dynamic Light Scattering (DLS)



Dynamic Light Scattering (DLS)

Number, volume and intensity distributions of a bimodal mixture of 5 and 50 nm lattices present in equal numbers
ISO 13321: Z-average (Intensity-derived) and polydispersity index (PdI)



DLS Technical note, Malvern Instruments

Dynamic Light Scattering (DLS)

Results confirmed by two independent laboratories

Swiss Federal Laboratories for Materials Science and Technology (EMPA, Switzerland)

University of Braunschweig (Germany)

Hydrodynamic diameter in Number for Venofer and different Similars A - G.
*(n=3, * P ≤ 0.05)*

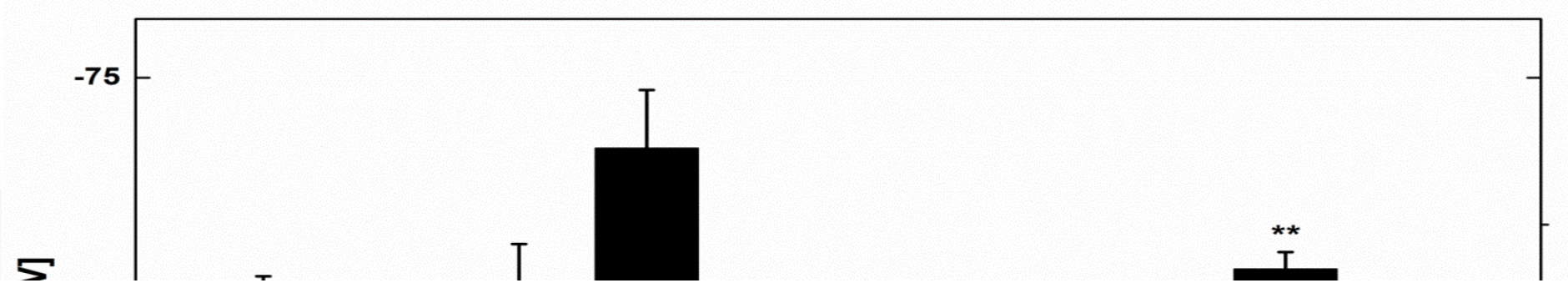
Zeta Potential

Iron carbohydrate drug solutions prepared at the concentration of 0.2 mg Fe/mL using Aqua B Braun.

Treatment for 2 h with Chelex® resin (40 mg resin/mL) under gentle stirring (100 rpm), to remove free iron in the solutions.

Supernatants introduced in Malvern DTS1070 disposable cells (~1 mL) and zeta potential values were obtained using *"Monomodal"* analysis model.

Zeta Potential



Results confirmed by two independent laboratories

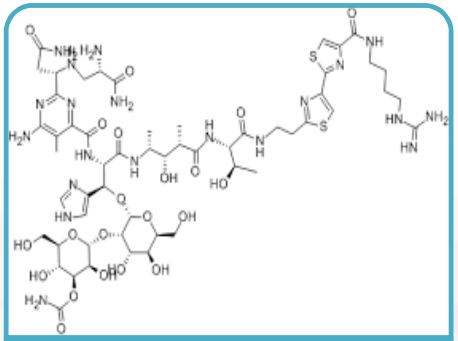
Swiss Federal Laboratories for Materials Science and Technology (EMPA Switzerland)

University of Braunschweig (Germany)

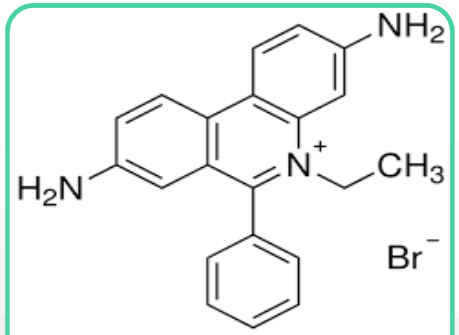
Zetapotential values for Venofer and different Similars A - G.

*(n=9, * P ≤ 0.05, ** P ≤ 0.01)*

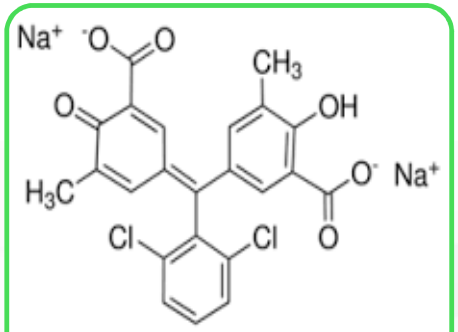
Determination of labile iron



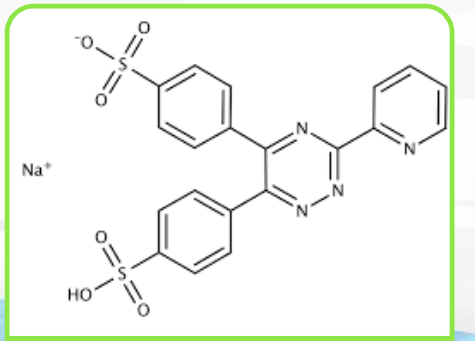
Bleomycin assay



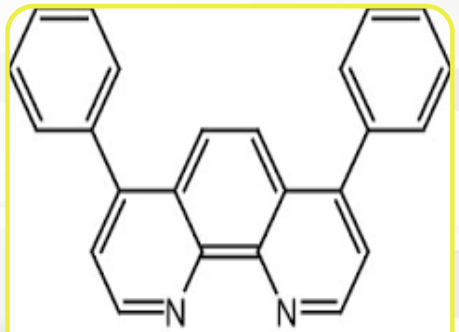
Bleomycin assay with ethidium bromide



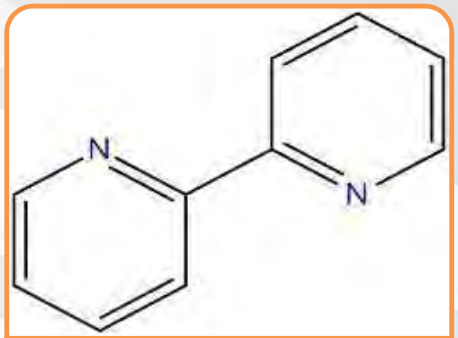
Chromazurol B assay



Ferrozine assay



Bathophenanthroline assay



2,2'- bipyridyl assay

Determination of labile iron

Assay					
Bleomycin	Bleomycin with ethidium bromide	Chromazurol B	Ferrozine	Bathophenan-throline	2,2'-bipyridyl
Commonly used to determine NTBI in serum samples	Improvement of bleomycin assay	Kit commercially available	Kit commercially available	Method to determine labile iron in iron carbohydrate drugs	Cheap
	Use of fluorescence	Linearity proven	Linearity proven		Fast
		Reproducible results	Reproducible results		
Linearity not proven	Linearity not proven	Mild method No reduction step needed	Harsh method Reduction agent may be too strong	Robustness not proven	Linearity not proven
Reagents not well water soluble				Results not reproducible	
Side reactions with lipid hydroperoxides in human samples	Toxicity of bleomycin			Expensive	
Toxicity of bleomycin	Toxicity of ethidium bromide			Harsh method Reduction agent may be too strong	

Chromazurol B Assay

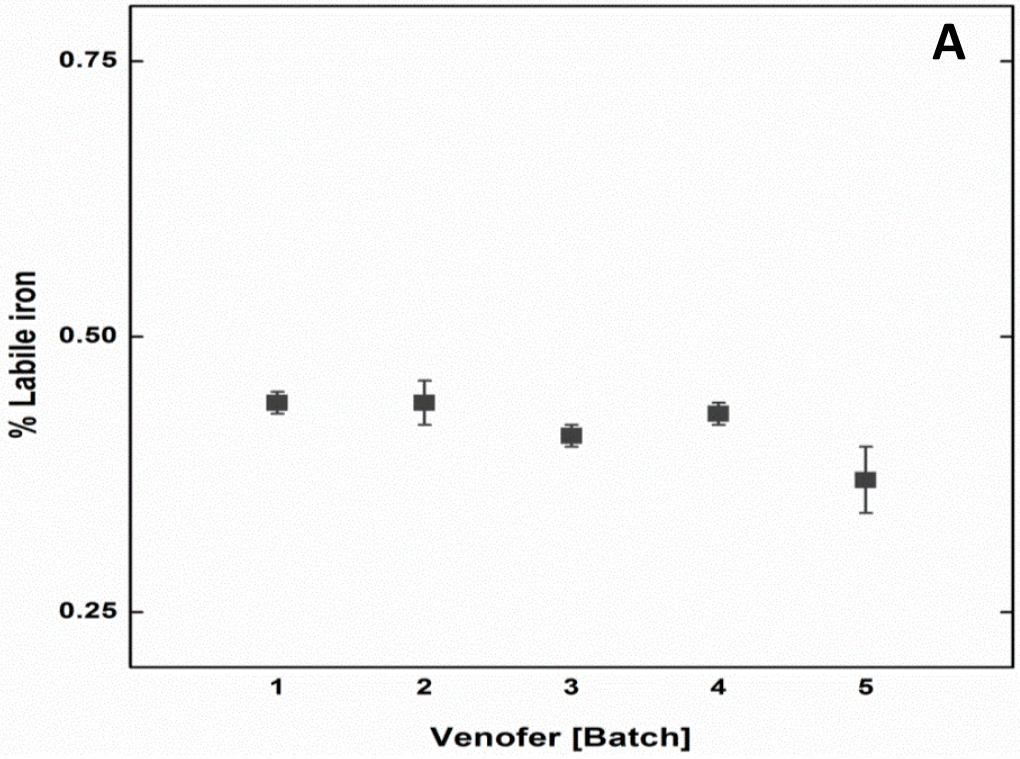
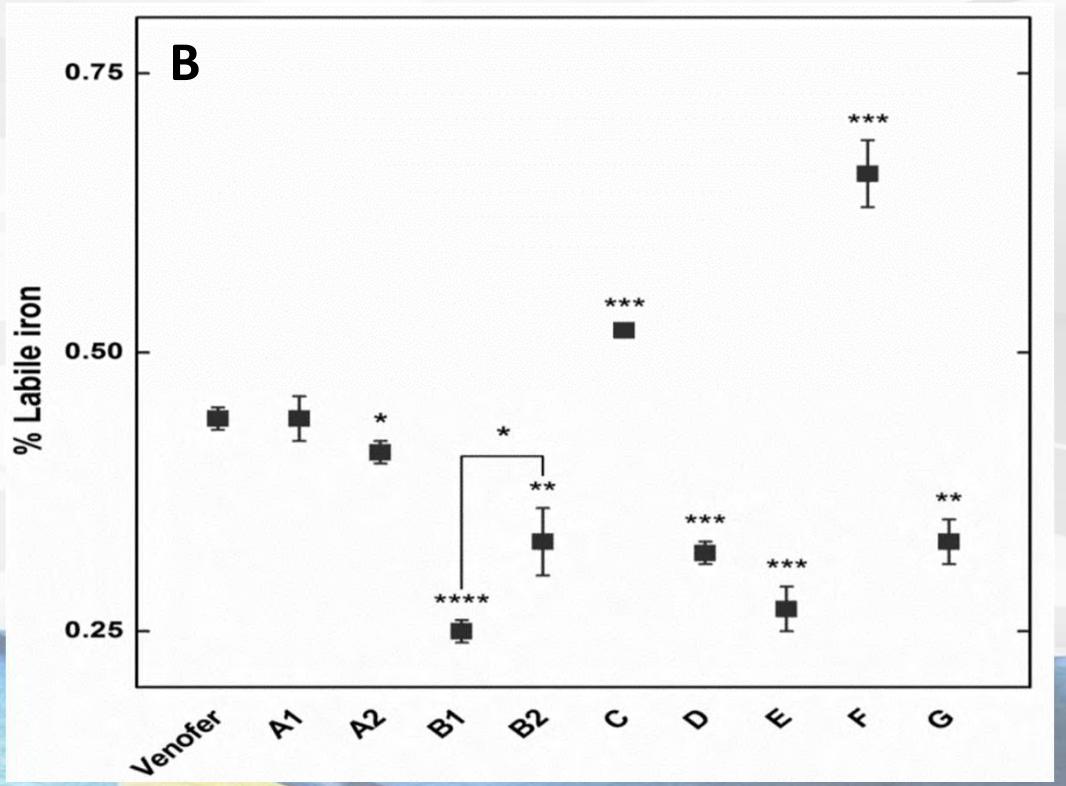


Fig A: Amount of labile iron for different batches of Venofer.

Fig B: Amount of labile iron for Venofer and different similars.
*(n=3, * P ≤ 0.05, ** P ≤ 0.01, *** P ≤ 0.001 and **** P ≤ 0.0001)*



Conclusions and perspectives

- Data analysis and presentation is essential
- Successfully developed protocols for DLS and Zeta Potential assays, confirmed by two independent laboratories
- Assays sufficiently sensitive to show differences between products and batch-to-batch
- Consider as 1st step in sequence:

  Quality assessment -> non-clinical (biodistribution) -> clinical trials
- Link quality assessment to clinical outcome
- Serve to monitor and control manufacturing process of non-biological complex drugs (NBCDs)

Thanks to:

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Members of the NBC Working Party

edqm European Directorate for the Quality of Medicines & HealthCare

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