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

PPCI
Pro Pharma Communications International

Non Biological Complex Drugs working group

lygature

FDA and EMA: Regulatory Situation of NBCDs

Beat Flühmann PhD,

Siem Reap May 18th 2016

GaBI Educational Workshops in collaboration with the NBCD Working Group

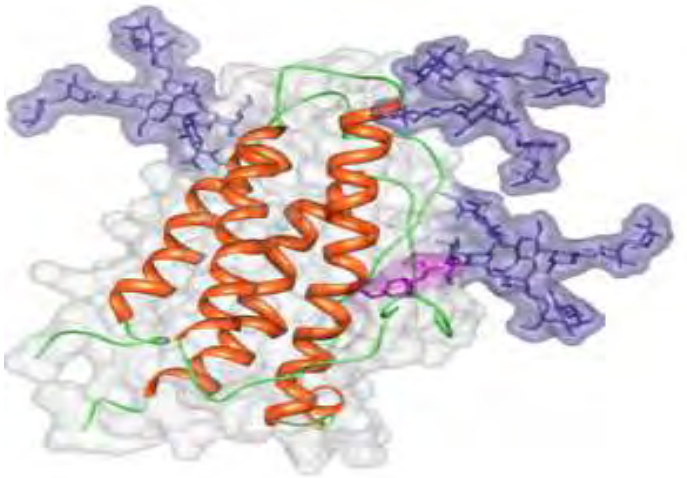
The Generic Paradigm → Sameness

- Pharmaceutical equivalence (identical API…)
- Bioequivalence in healthy subjects: comparable PK
- Known mode of action (PK ≈ PD)

No clinical efficacy and safety studies required

Generics:
Sameness

Classes of products

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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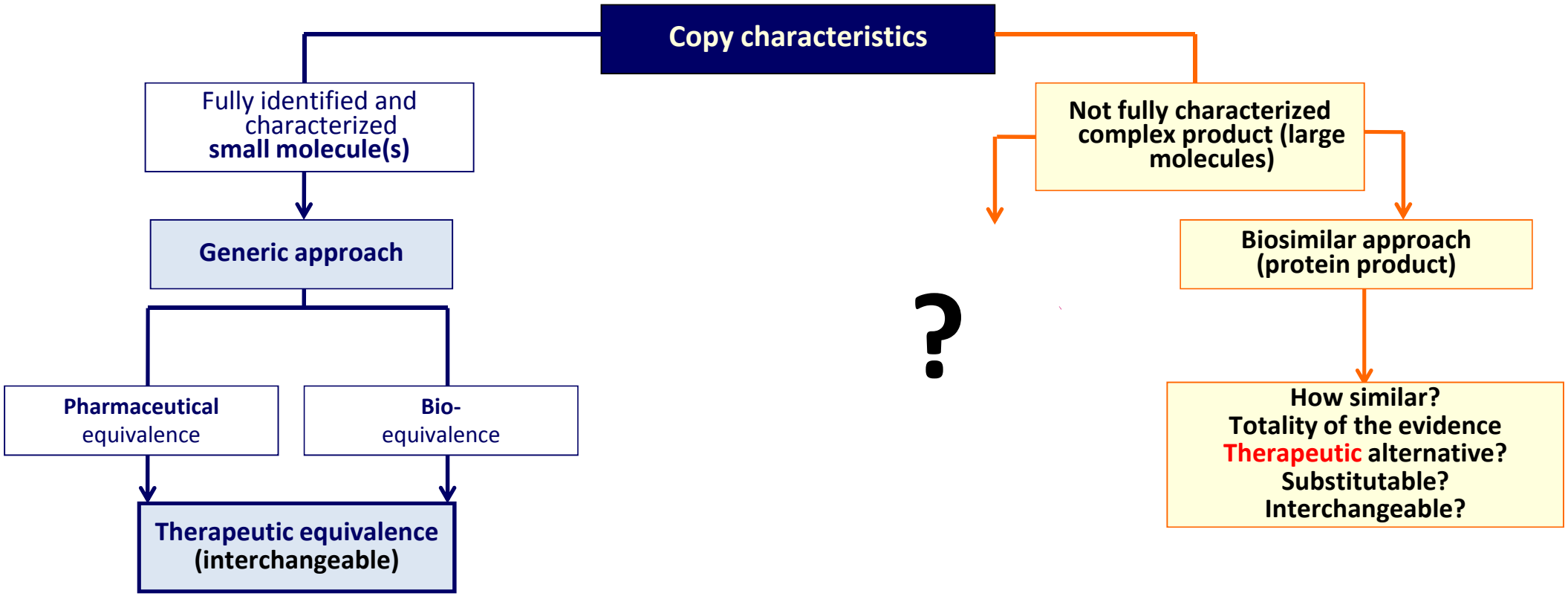
Todays Regulatory Pathways



Ref: DJA Crommelin et al., European J Pharm Sci. 76 (2015) 10–17

lygature

Scientific discussions initiated 6 years ago..

Workshop

Bioequivalence of Complex Drugs

7 October 2009, Leiden, the Netherlands

"the Leiden Paper"

Regulatory Toxicology and Pharmacology 59 (2011) 176–183

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

The therapeutic equivalence of complex drugs ☆

Huub Schellekens [a,b,*], Ety Klinger [c,1], Stefan Mühlebach [d,2], Jean-Francois Brin [e,3], Gert Storm [f,g], Daan J.A. Crommelin [f,g,h,i]

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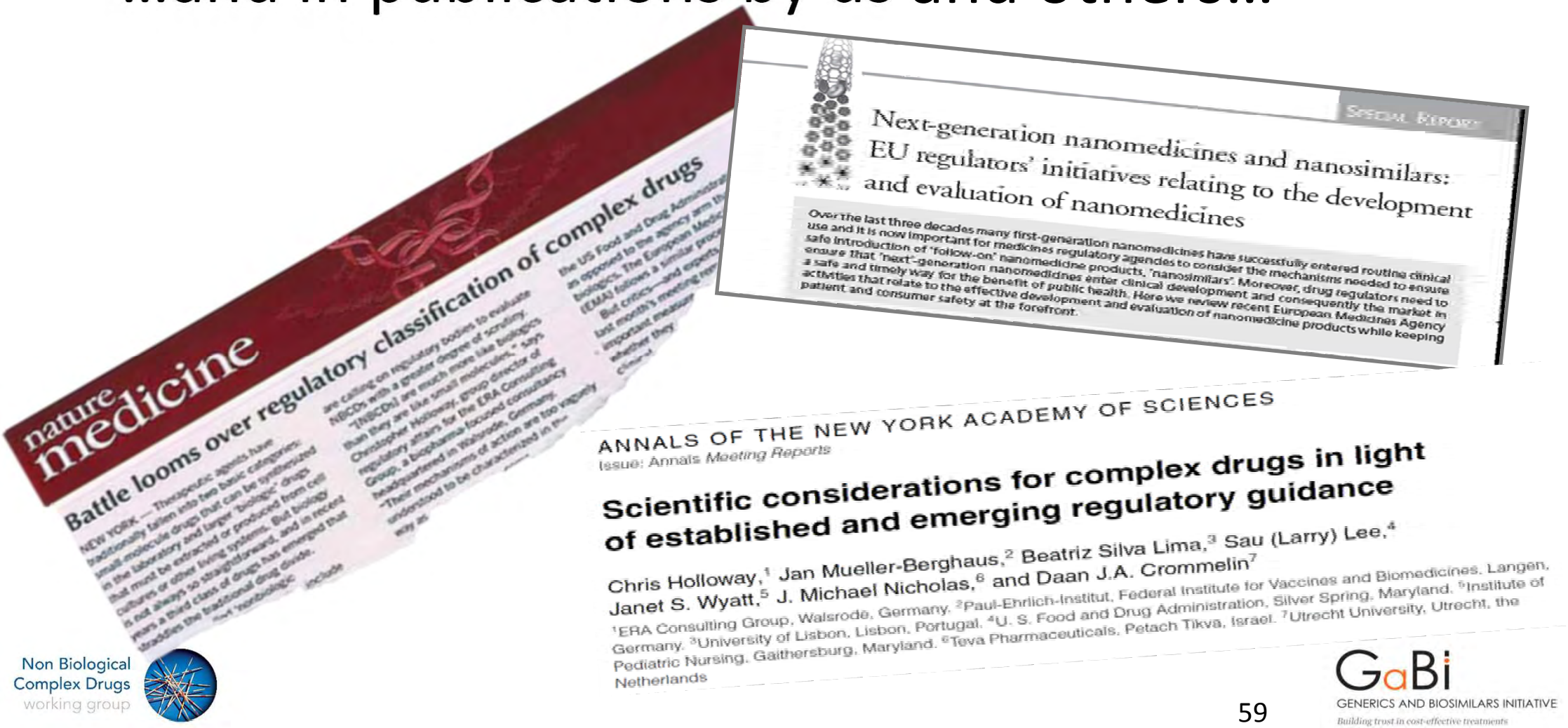
…and in publications by us and others…



nature medicine

Battle looms over regulatory classification of complex drugs

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

Special Report

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Issue: Annals *Meeting Reports*

Scientific considerations for complex drugs in light of established and emerging regulatory guidance

Chris Holloway,[1] Jan Mueller-Berghaus,[2] Beatriz Silva Lima,[3] Sau (Larry) Lee,[4] Janet S. Wyatt,[5] J. Michael Nicholas,[6] and Daan J.A. Crommelin[7]

[1]ERA Consulting Group, Walsrode, Germany. [2]Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines, Langen, Germany. [3]University of Lisbon, Lisbon, Portugal. [4]U. S. Food and Drug Administration, Silver Spring, Maryland. [5]Institute of Pediatric Nursing, Gaithersburg, Maryland. [6]Teva Pharmaceuticals, Petach Tikva, Israel. [7]Utrecht University, Utrecht, the Netherlands

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…and in publications by us and others.

The AAPS Journal (© 2013)
DOI: 10.1208/s12248-013-9532-0

Commentary

Different Pharmaceutical Products Need Similar Terminology

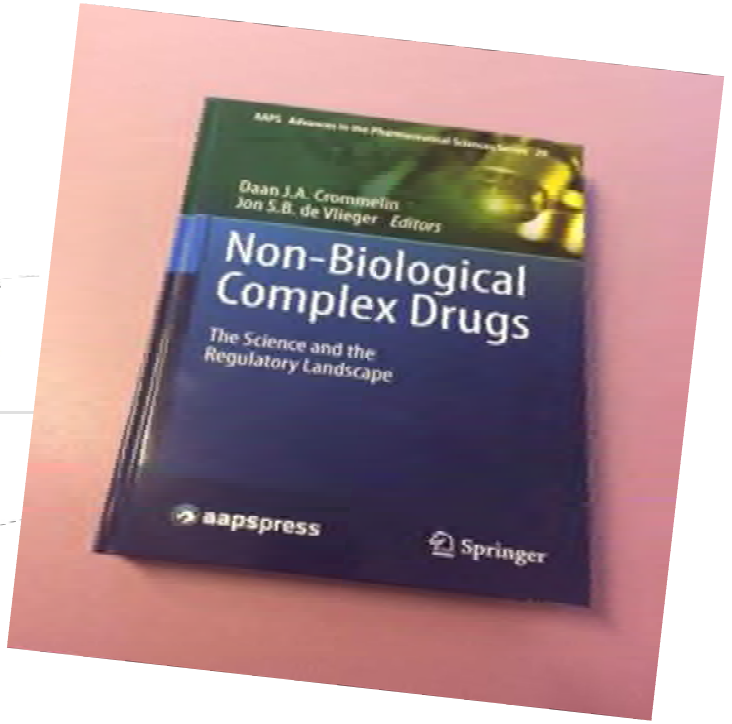
Daan J. A. Crommelin,[1] Jon S. B. de Vlieger,[2] Vera Weinstein,[3] Stefan Mühlebach,[4] Vinod P. Shah,[5]

The AAPS Journal (© 2013)
DOI: 10.1208/s12248-013-9533-z

Commentary

How to Regulate Nonbiological Complex Drugs (NBCD) and Their Follow-on Versions: Points to Consider

Houb Schellekens,[1,2,10] Sven Stegemann,[3] Vera Weinstein,[4] Jon S. B. de Vlieger,[5] Beat Flühmann,[6] Stefan Mühlebach,[7] Rogério Gaspar,[8] Vinod P. Shah,[9] and Daan J. A. Crommelin[1]



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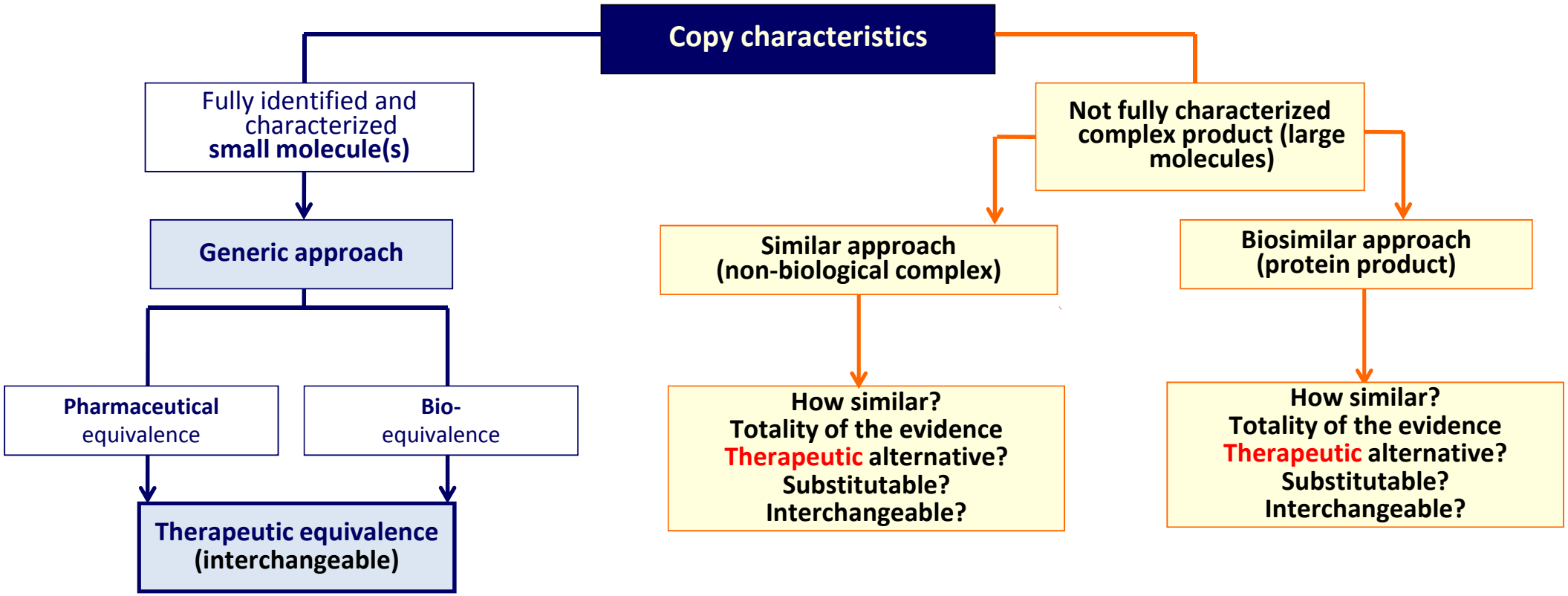
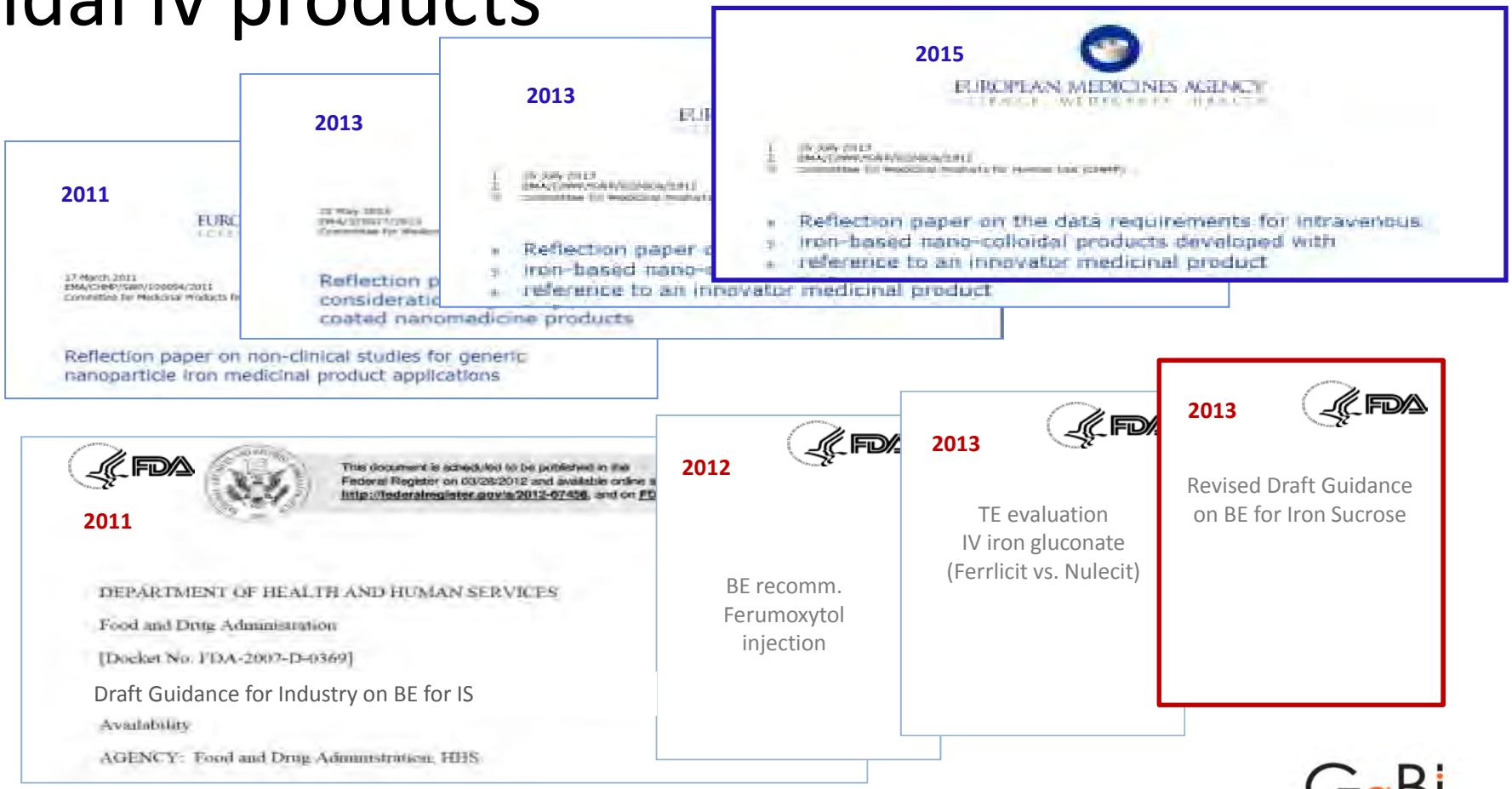
Follow the Similarity Approach.



Ref: DJA Crommelin et al., European J Pharm Sci. 76 (2015) 10–17

EMA and FDA issued proposals for nano colloidal iv products



FDA aware of complexity of products

- Quality
  - Iron release influenced by size morphology and surface properties (quality, toxicity)
  - Carbohydrate coating properties (kinetics, hypersensitivity, safety, impurities)
  - Labile iron release under physiological conditions
- Pharmaceutical comparability
  - Chemical composition and physicochemical characteristics
  - Manufacturing controls
- Clinical
  - Bioequivalence

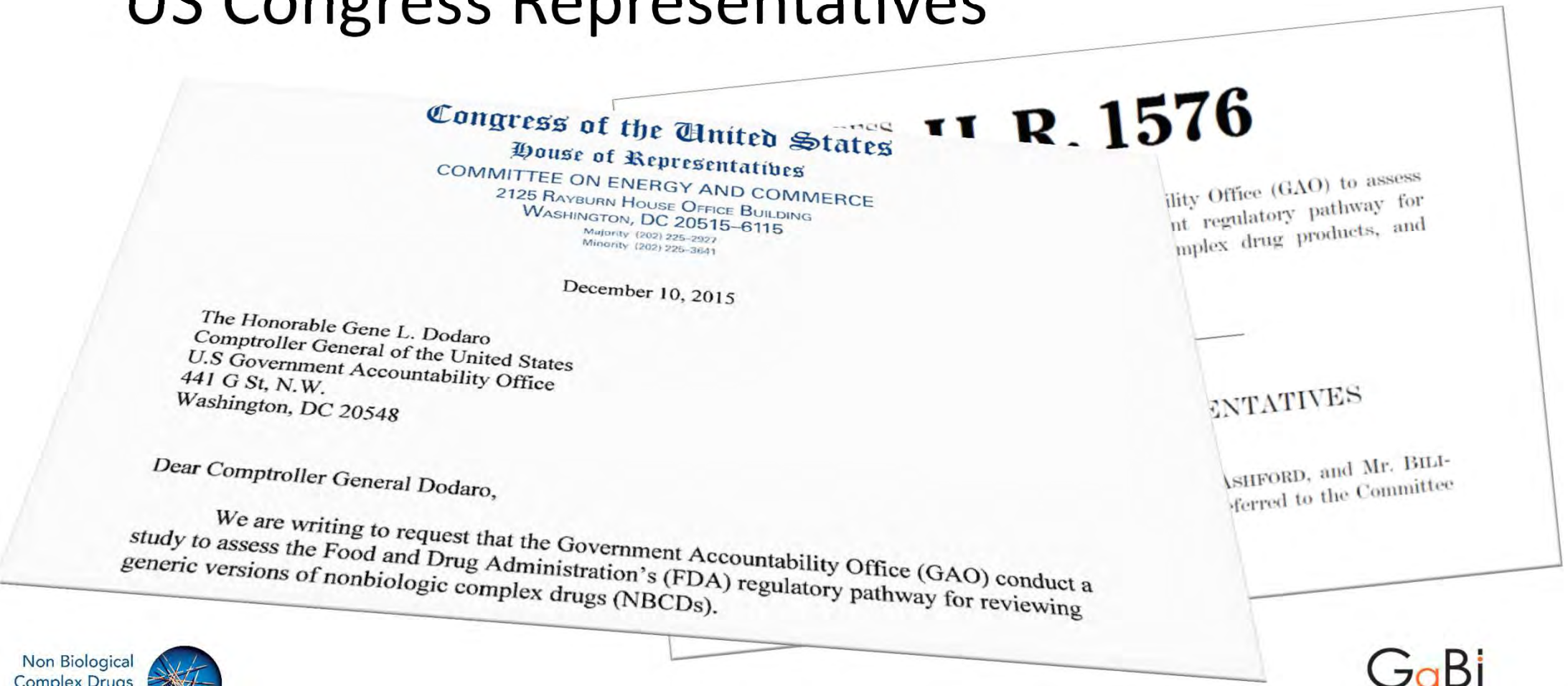
GDUFA Regulatory Science Priorities 2016

- Post-market evaluation of generic drugs
- **Equivalence of complex products**
- Equivalence of locally-acting products
- Therapeutic equivalence evaluation and standards
- Computational and analytical tools

FDA and NIH initiated a research program to link FDA's equivalence standards to in vivo performance including clinical trials

http://www.fda.gov/GDUFARegScience

NBCDs Approval Process Under Scrutiny by US Congress Representatives



Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115
Majority (202) 225–2927
Minority (202) 225–3641

December 10, 2015

The Honorable Gene L. Dodaro
Comptroller General of the United States
U.S Government Accountability Office
441 G St, N.W.
Washington, DC 20548

Dear Comptroller General Dodaro,

We are writing to request that the Government Accountability Office (GAO) conduct a study to assess the Food and Drug Administration's (FDA) regulatory pathway for reviewing generic versions of nonbiologic complex drugs (NBCDs).

H. R. 1576

lity Office (GAO) to assess
nt regulatory pathway for
mplex drug products, and

ENTATIVES

ASHFORD, and Mr. BILI-
ferred to the Committee

EMA considerations on Nanosimilars

- Quality
  - Iron release influenced by size morphology and surface properties (quality, toxicity)
  - Carbohydrate coating properties (kinetics, hypersensitivity, safety, impurities)
- Pharmaceutical comparability
  - Chemical composition and physicochemical characteristics (stress tests)
  - Manufacturing controls
- Non-clinical
  - Blood/plasma, RES, and tissue concentration comparisons
  - Biodisposition in animal model incl. “toxicological” target tissues
- Clinical
  - PK
  - Efficacy and short-time safety (only if minor differences observed)
- PV

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http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/09/WC500149496.pdf

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