Non-Biological Complex Drugs

Challenges for approval standards

and opportunities!!

Vinod P. Shah, PhD

Steering Committee Member NBCD – Working Group

Non Biological Complex Drugs working group

The NBCD working group has the mission to ensure that **appropriate *science*-based approval and post-approval standards are created and globally introduced for NBCDs to ensure patient safety and benefit**.

Current partners are the US NCI Nanotechnology Characterization Lab, the University of Geneva, Allergan Plc, and Vifor International Inc.

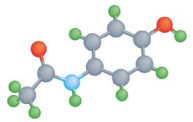
Hosted by Lygature, a not-for-profit organization based in the Netherlands, the working group consists of experts from industry, academia, and knowledge institutes.

In addition to in-kind contribution of all partners, funding is provided by Allergan Plc and Vifor International Inc.

http://www.lygature.org/NBCD

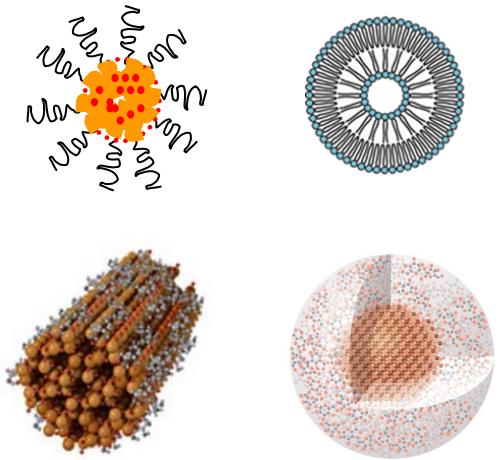
The rise of bio- and nano-technologies has accelerated the development of complex medicines

Conventional drugs



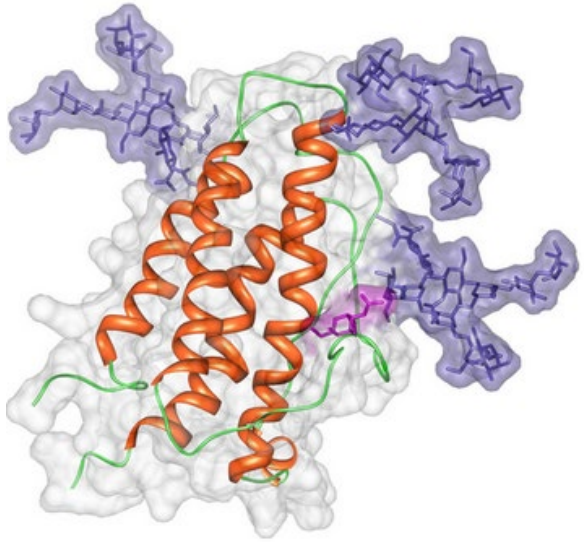
Small molecule drugs
(MW <500d*)*
e.g. ASA
Fully characterized

(Nano) technology



Complex (non-biological) drugs
e.g. polynuclear ferric hydroxide carbohydrate complexes, glatiramoids, liposomes,…
Not fully characterized

Biotechnology drugs

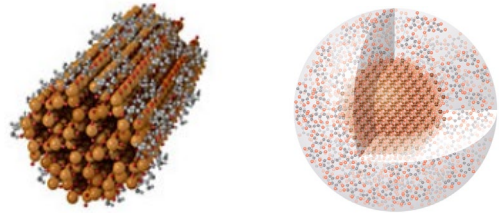


Complex (biological) drugs
(MW range 5-150kDa)
e.g. *EPO*
Not fully characterized

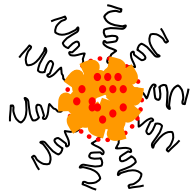
A non-biological complex drug product……

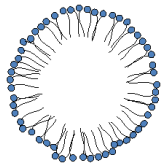
- … is a synthetic medicinal product that is **not a biological medicine**
- … with an active substance that is **not homo-molecular** but contains different (closely related, often nano-particulate) structures
- … that **cannot be fully characterized** by physicochemical analytical means.

A **well-controlled** robust manufacturing process is fundamental to ensure quality, safety and efficacy.



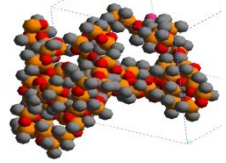
Iron-carbohydrate complexes



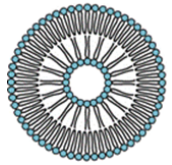


Micelles

Nanoemulsions



Polymers



Liposomes

Dendrimers

Full definition NBCD:Crommelin et al. Different pharmaceutical products need similar terminology; AAPS J. 2014

Therapeutic Equivalence for Generic and Similar Products

PE + BE = TE = TI

The major challenge for NBCDs is to establish the equivalence – PE and/or BE

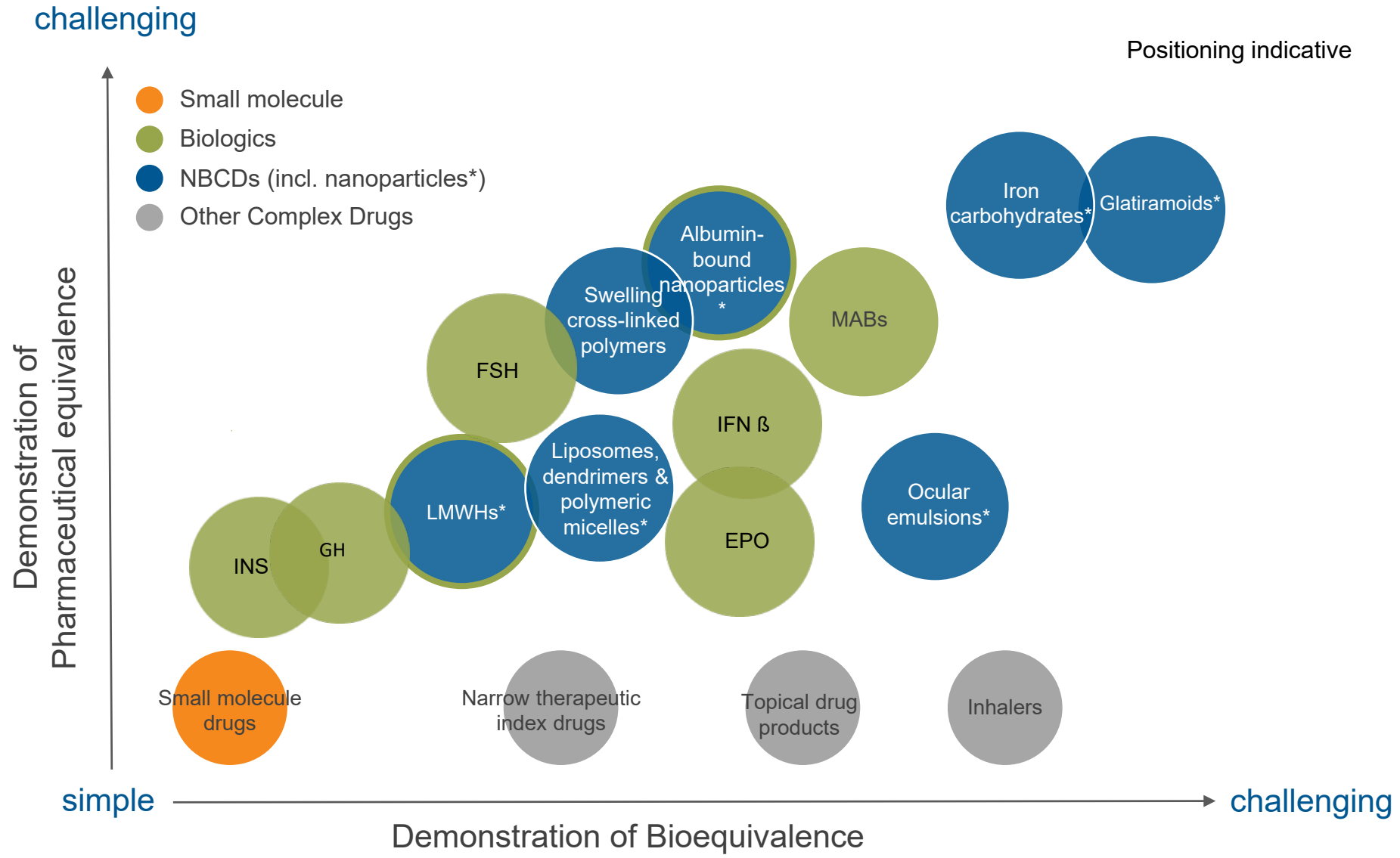
Another challenge is Regulatory Pathway Harmonization

(between US and EU/EMA)

NBCDs- Recent developments

- **GAO Report**, Jan 2018:
  Scientific challenges involved when demonstrating equivalence
- **AAPS Guidance Forum Workshop**, Sept 2018:
  Draft Guidance – Drug products, including biological products, that contain nanomaterials, Dec 2017. **- Regulatory Approval Pathway -**
  Workshop Report – The AAPS Journal April 2019
- **FDA/PQRI workshop** April 9-11, 2019:
  - Both biosimilars and non-biological complex drug (NBCD) products achieving similarity should be based on ‘a stepwise approach and totality of evidence’.
  - Are the present pathways for the approval of NBCD products adequate?
  - Time for a new look at the Hatch Waxman act (cf. Gottlieb)?

The group of complex drug products is diverse, the NBCDs form a subgroup



Adapted from de Vlieger et al. The AAPS Journal (2019) 21:56

Non Biological Complex Drugs working group

Worldwide discussions on whether current regulatory frameworks for NBCDs are fit for purpose

ELSEVIER

European Journal of Pharmaceutical Sciences

Volume 133, 15 May 2019, Pages 228-235

The EU regulatory landscape of non-biological complex drugs (NBCDs) follow-on products: Observations and recommendations

K. Klein [a, b, c], P. Stolk [a, b, c], M.L. De Bruin [a, d], H.G.M. Leufkens [a, b], D.J.A. Crommelin [e], J.S.B. De Vlieger [b]

Show more

US GAO Report on NBCDs

Generic Versions of NBCDs Pose Scientific Challenges during the Drug Development Process; FDA Considered Multiple Types of Equivalency Data in Its Approvals

Stakeholders We Interviewed Agreed that Demonstrating Equivalence between Brand and Generic NBCDs Is Scientifically Challenging, but Disagreed about Whether Challenges Can Be Overcome

Suggestions are made to look into legislation (EU)

From: EMA on CLINAM 2018 Basel

Aspects for consideration

- There is no legal definition in EU of 'complex hybrids'
- Develop timely common understanding on what constitutes 'complex hybrids'
- EMA supports to engage in a reflection on a global development approach for 'complex hybrids'
- Explore, within regulatory framework boundaries, the possibility to use a non-EEA comparator (representative of the RefMP) for supportive non-clinical/clinical studies

Suggestions are made to look into legislation (US)

Gottlieb: Changes To Hatch-Waxman May Boost Complex Generic Market

April 04, 2019

"The one place is looking at complex formulations of complex drugs where sometimes from a scientific standpoint it's hard to develop generic copies of those drugs and demonstrate they're the same through a conventional regulatory process," Gottlieb explained. "**You could contemplate changes to the Hatch-Waxman construct that allows the agency to look at small complements of clinical data in the context of an approval of a complex drug.** You'd have to go through the difficult job of defining what a complex drug is. I can define what I know it is. Sometimes it's harder to define what you know it isn't."

Both sides discuss alignment and harmonization (EU)

From: EMA on CLINAM 2018 Basel

EUROPEAN MEDICINES AGENCY

Investigation of a global development approach for 'complex hybrids'

- In July 2016, EMA approached FDA to understand US requirements for "complex generics" and explore possibilities for global development

- In June 2017 reflection with the EC from regulatory perspective on acceptability of a global development approach for 'complex hybrids'

Both sides discuss alignment and harmonization (US)

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Advancing Toward the Goal of Global Approval for Generic Drugs: FDA Proposes Critical First Steps to Harmonize the Global Scientific and Technical Standards for Generic Drugs

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October 18, 2018

By: Scott Gottlieb, M.D.

In particular, to fill these gaps, we're proposing that ICH develop a series of guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for both non-complex dosage forms, and for more complex dosage forms and drug products.

Complex Drugs – NBCD desired state

- Science based approach for generic/similar NBCD products – ‘NBCD similar’
- Universally acceptable ‘similarity’ pathway
- Global harmonization of scientific and technical requirements for generic drugs would benefit stakeholders
- Stepwise comparison of Test and Ref products at all stages to avoid non-comparability in clinical studies and to facilitate interchangeability
- Assure TE of new complex generic/similar (NBCDs)
- Avoid non-equivalence in Efficacy and Safety

Only with involvement of all stakeholders we can ensure a fit for purpose framework

AWARENESS

Stakeholders become aware of intricacies of the structures of NBCDs and their scientific, regulatory and clinical implications

UNDERSTANDING

The Critical Quality Attributes (CQA) for NBCDs are being identified, resulting in appropriate regulatory guidance documents; pharmacovigilance systems and practice are fit for purpose

ALIGNMENT

Stakeholders across the globe agree on the science, regulation and clinical application of NBCDs

Complex Medicines: Science, Regulation, and Accelerating Development

nyas.org/ComplexMedicines2019

#ComplexMedicines2019

May 13, 2019
8:00 AM – 6:00 PM
The New York Academy of Sciences

This symposium will outline the future of complex medicines, including the best scientific approaches for their development and regulation, challenges in the assessment of equivalence, and how to ensure timely access for patients.

Presented By:

Non Biological Complex Drugs working group

The New York Academy of Sciences

NCL Nanotechnology Characterization Laboratory