Nanomedicines: Industry Perspective

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Steering Committe Member NBCD Consortium
Lygature

The reality of nanomedicine

What makes them different?

Challenges in Drug Development

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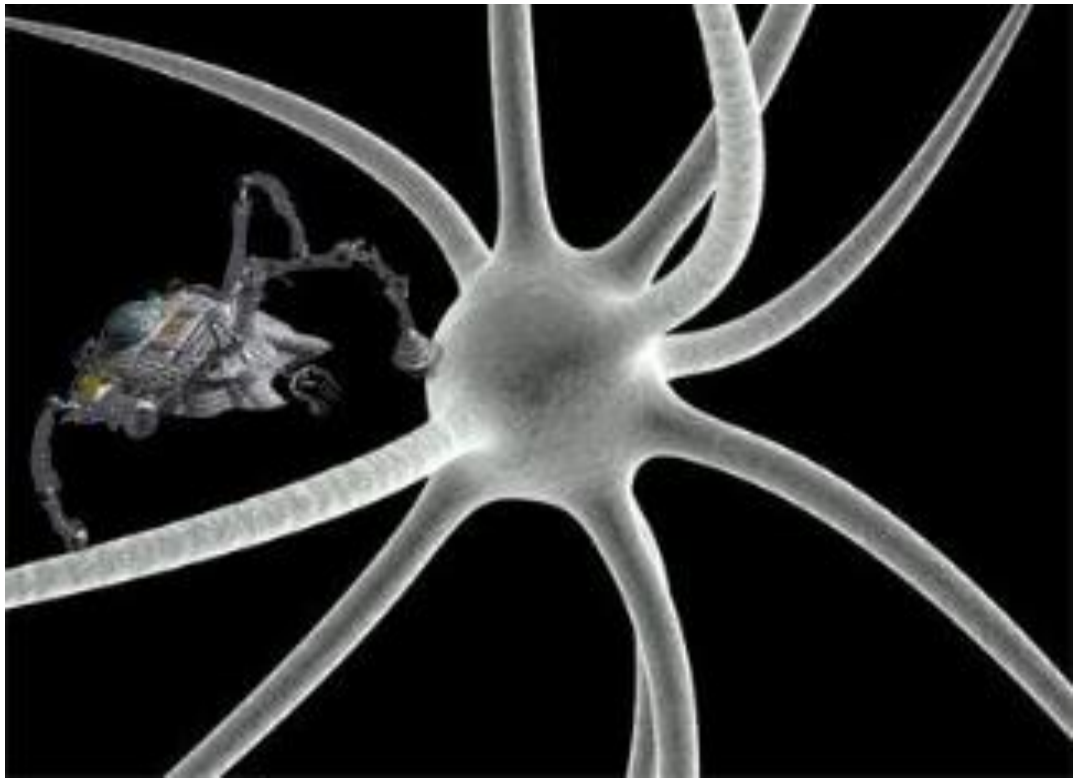
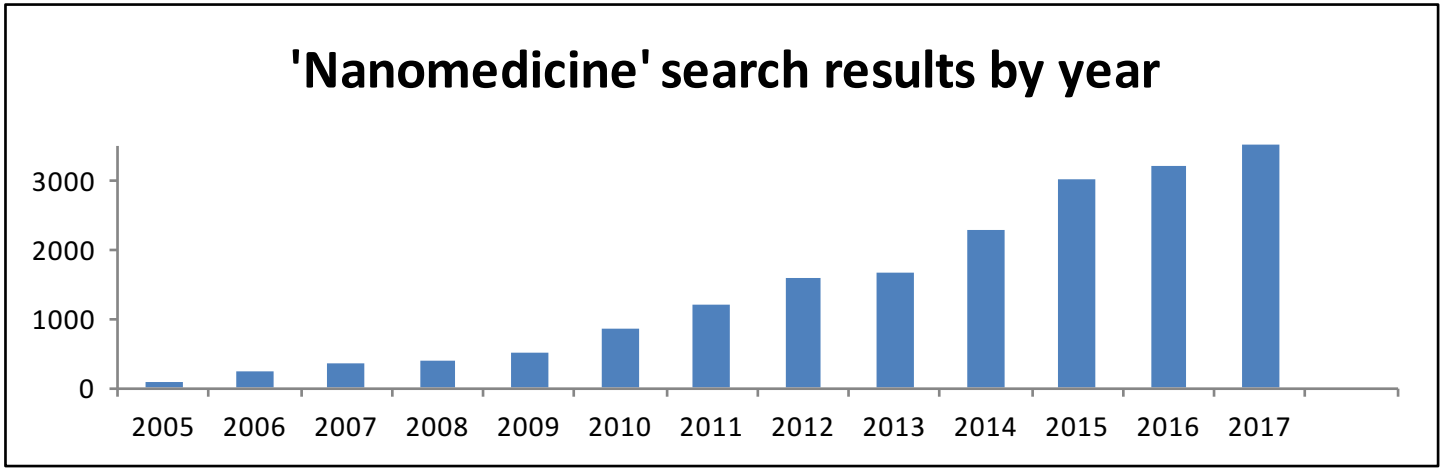
Challenges in Drug Development

Are nanomedicines science fiction or reality?



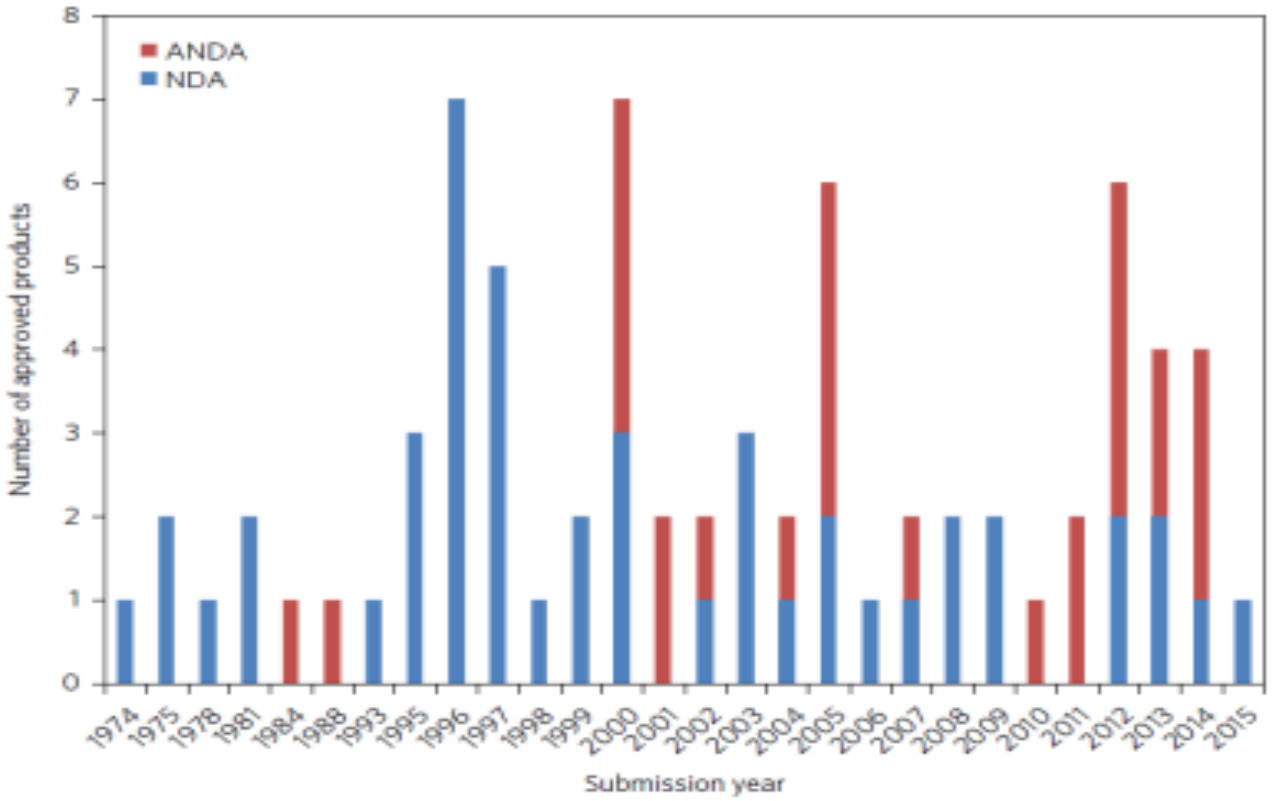
Are nanomedicines science fiction or reality?

- PubMed.gov returns 19431 results to the term ‘nanomedicine’, as of April 2018. Publications in field, currently focus more on safety and efficacy.



- As of April 2018, out of the 182 clinical trials including the term “nano”, 53 were listed as “recruiting” or “active, not recruiting” on ClinicalTrials.gov.

Are nanomedicines science fiction or reality?



Crommelin and de Vlieger, Non-biological complex drugs, Springer 2015

D'Mello, S. R., Cruz, C. N., Chen, M. L., Kapoor, M., Lee, S. L., & Tyner, K. M. The evolving landscape of drug products containing nanomaterials in the United States. Nat. Nanotechnol. 12, 523-529 (2017).

Nanopharmaceuticals, a selection…

[1]AmBisome®
- Fungal/Protozoal infections
- Liposomal amphotericin B
- Gilead Sciences

[4]Rapamune®
- Immunosuppressant
- Sirolimus
- Wyeth Pharmaceuticals

[7]Restasis®
- Chronic dry eye disease
- Cyclosporine ophthalmic emulsion
- Allergan

[5]Venofer®
- Anaemia
- Iron sucrose
- Vifor Pharma

[3]Copaxone®
- Multiple sclerosis
- Glatiramer acetate
- Teva Pharmaceuticals

[2]Doxil®
- Cancer
- Doxorubicin liposomal
- Janssen

[6]Abraxane®
- Cancer
- Albumin-bound paclitaxel
- Celgene

1https://sydala.com/products/ambisome 2https://www.empr.com/news/doxil-injection-long-term-supply-available/article/270755/
3https://www.neurologyadvisor.com/multiple-sclerosis/teva-supreme-court-ruling-copaxone-patent/article/393999/ 4https://yaoota.com/en-eg/product/rapamune-1-mg-30-tab-price-from-seif-egypt 5http://www.oncologydrugs.co.in/venofer-2736411.html
6https://pancreaticcanceraction.org/news/reappraisal-life-extending-drug-abraxane-treatment-advanced-pancreatic-cancer-take-place-30th-march-2016/
7https://rxzone.net/product/restasis-0.05-2/

The reality of nanomedicine

What makes them different?

Challenges in Drug Development

What is a Nanomedicine?

FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms. As described in FDA's nanotechnology considerations guidance (issued in June 2014), at this time, when considering whether an FDA-regulated product involves the application of nanotechnology, FDA will ask:

- (1) whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm).

Size

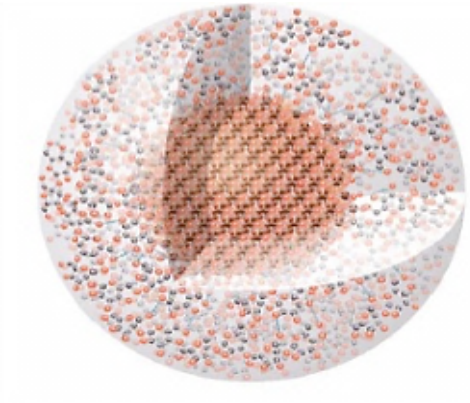
In addition, because materials or end products can also exhibit related properties or phenomena attributable to a dimension(s) outside the nanoscale range of approximately 1 nm to 100 nm that are relevant to evaluations of safety, effectiveness, performance, quality, public health impact, or regulatory status of products, we will also ask:

- (2) whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm).

Function

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 can lead to change in:



Same Composition But Different Particles Lead to Different Biology

- One determinant for the fate of nanomedicines is the interaction of the biological environment with their surface.
- Surface modification of nanoparticles can lead to change in:
  - Pharmacokinetics

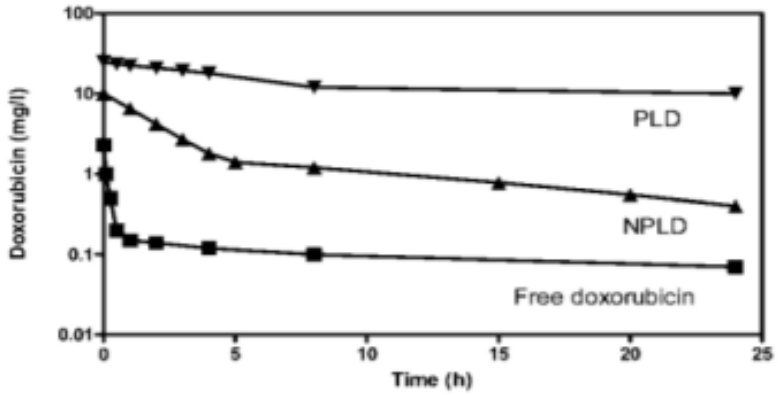
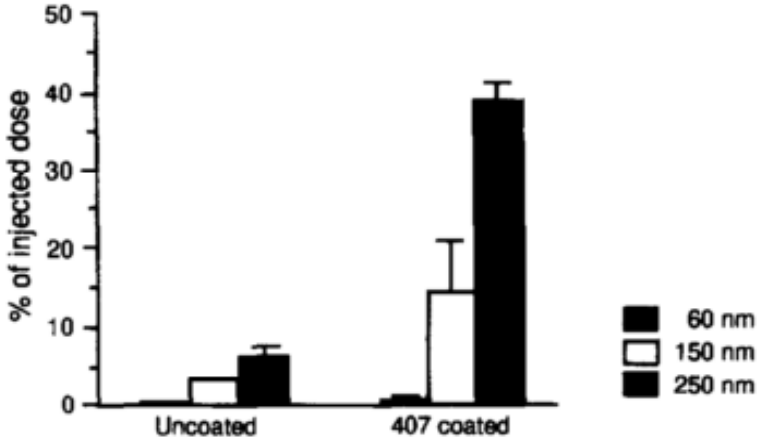


Fig. (6). Plasma mean concentrations of doxorubicin in patients receiving a single intravenous dose of PLD 50 mg/m^2 (14 patients), NPLD 60 mg/m^2 (10 patients), or free doxorubicin 50 mg/m^2 (4 patients) [81, 82].

Same Composition But Different Particles Lead to Different Biology

- One determinant for the fate of nanomedicines is the interaction of the biological environment with their surface.
- Surface modification of nanoparticles can lead to change in:
  - Pharmacokinetics
  - Organ disposition

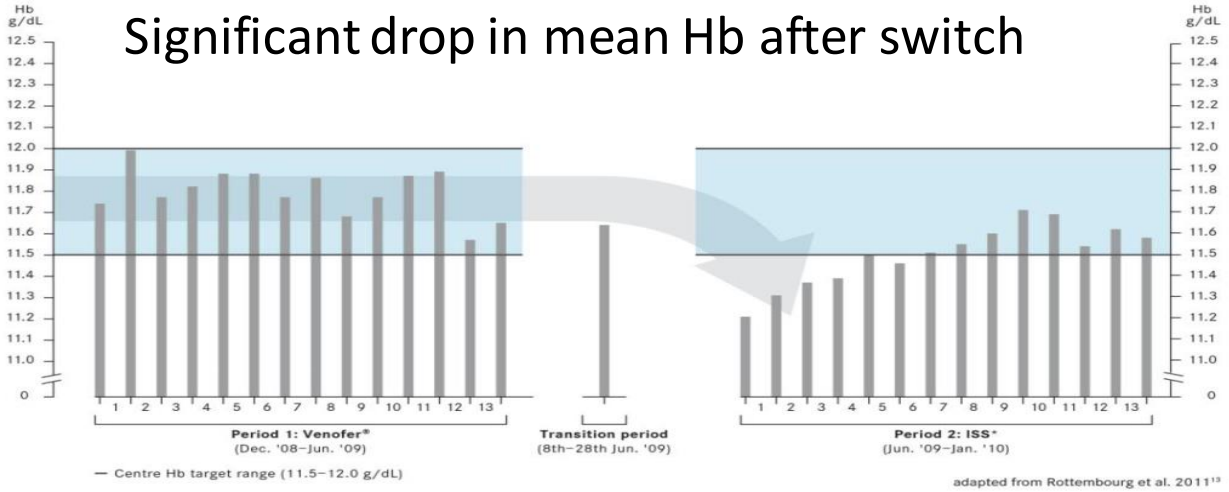


Effect of particle size on spleen uptake of poloxamer-407-coated polystyrene particles in rats[2]

[2]Storm G *et al*. (1995). Surface modification of nanoparticles to oppose uptake by the mononuclear phagocyte system. *Adv Drug Deliv Rev.* 17(1): 31-48

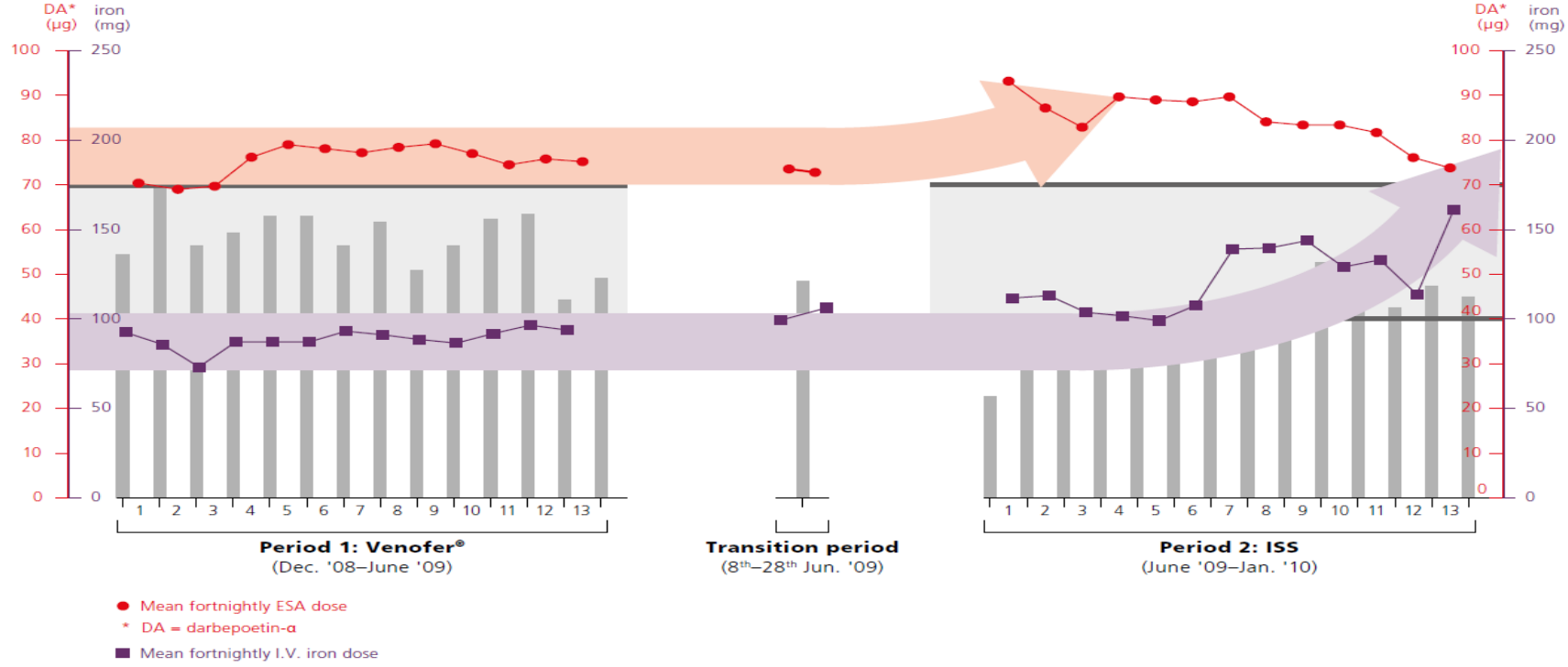
Same Composition But Different Particles Lead to Different Biology

- One determinant for the fate of nanomedicines is the interaction of the biological environment with their surface.
- Surface modification of nanoparticles can lead to change in:
  - Pharmacokinetics
  - organ disposition
  - Pharmacodynamics



Significant increase in mean I.V. iron consumption after switch from Venofer® to FerMylan®

34.6% increase in I.V. iron during P2 vs. P1 (p=0.001)
12.6% increase in mean ESA dose P2 vs. P1



Same Composition But Different Particles Lead to Different Biology

- One determinant for the fate of nanomedicines is the interaction of the biological environment with their surface.
- Surface modification of nanoparticles can lead to change in:
  - Pharmacokinetics
  - Organ disposition
  - Pharmacodynamics
  - Toxicity
  - Immunogenicity
  - Stability

Handling can affect physical stability and impact clinical outcome

Transport

- Temperature
- Light
- Vibration

Storage

- Temperature
- Light
- Duration

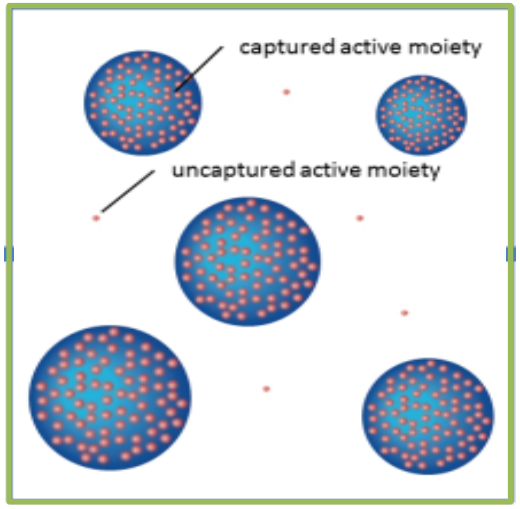
Ready to use prep.

- Diluent
- Dilution factor
- Packaging materials
- Temperature
- Light
- Storage duration

Administration

- Route of administration
- Administration speed

Distinct Physical Properties of Nanomedicines Need to be Considered During Storage and Handling

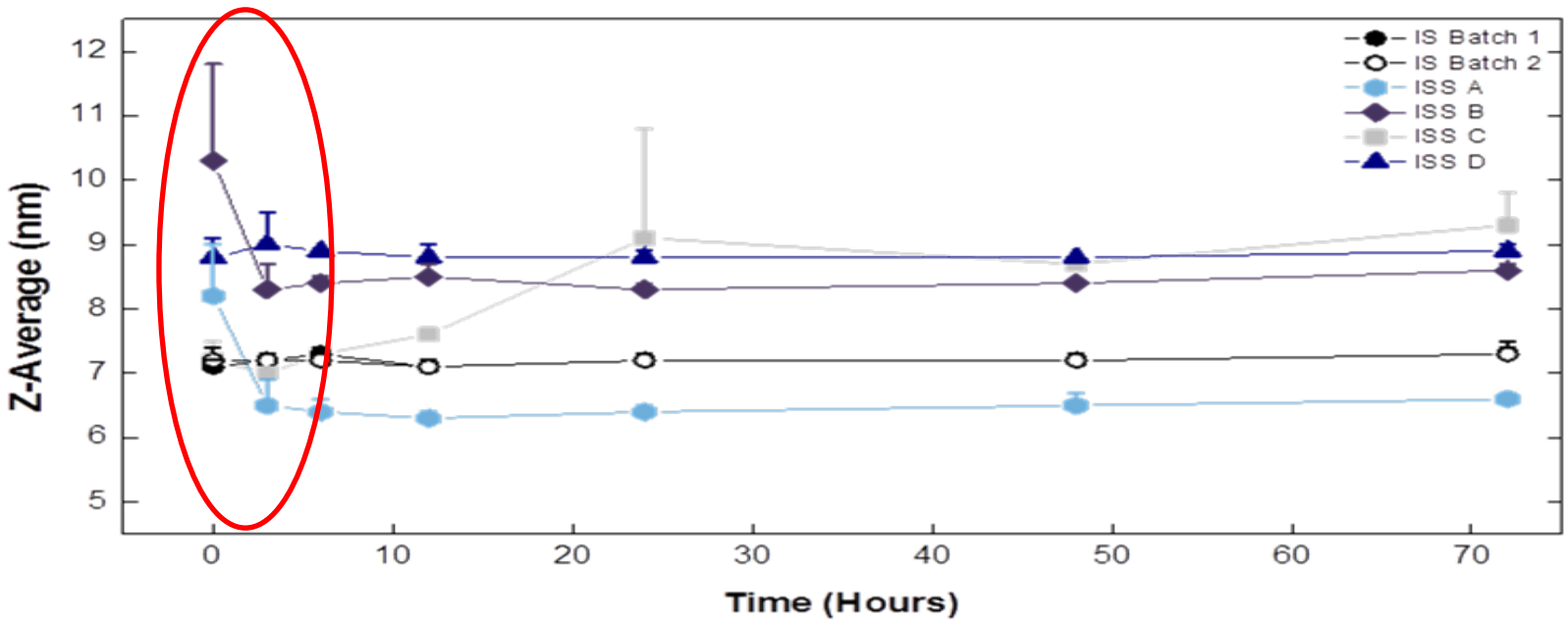


nanoparticle solution

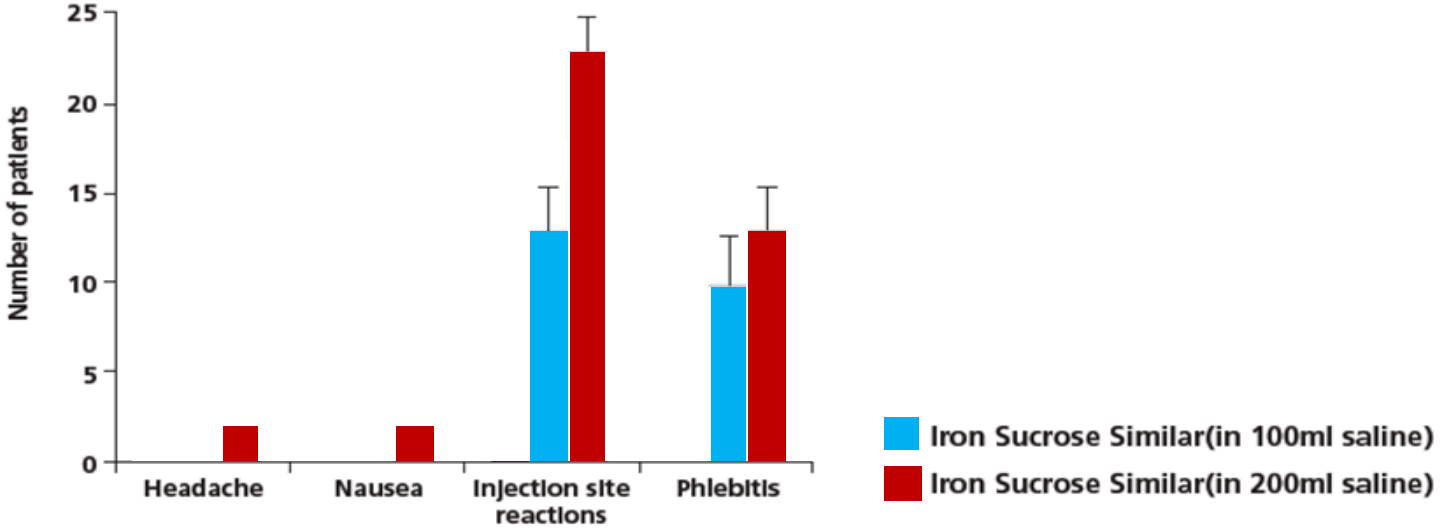
Dilution of Nanomedicines Can Destabilize Particles

Dilution of Nanomedicines Can Destabilize Particles

Preparation of ready to use infusion



Dilution of nanomedicines can destabilize particles And Impact the Safety Profile



Adapted from Lee *et al.* (2013) Comparison of adverse event profile of intravenous iron sucrose and iron sucrose similar in postpartum and gynecologic operative patients. *Curr Med Res Opin*. 29(2):141-7

The reality of nanomedicine

What makes them different?

Challenges in Drug Development

Critical quality attributes need to be clinically meaningful

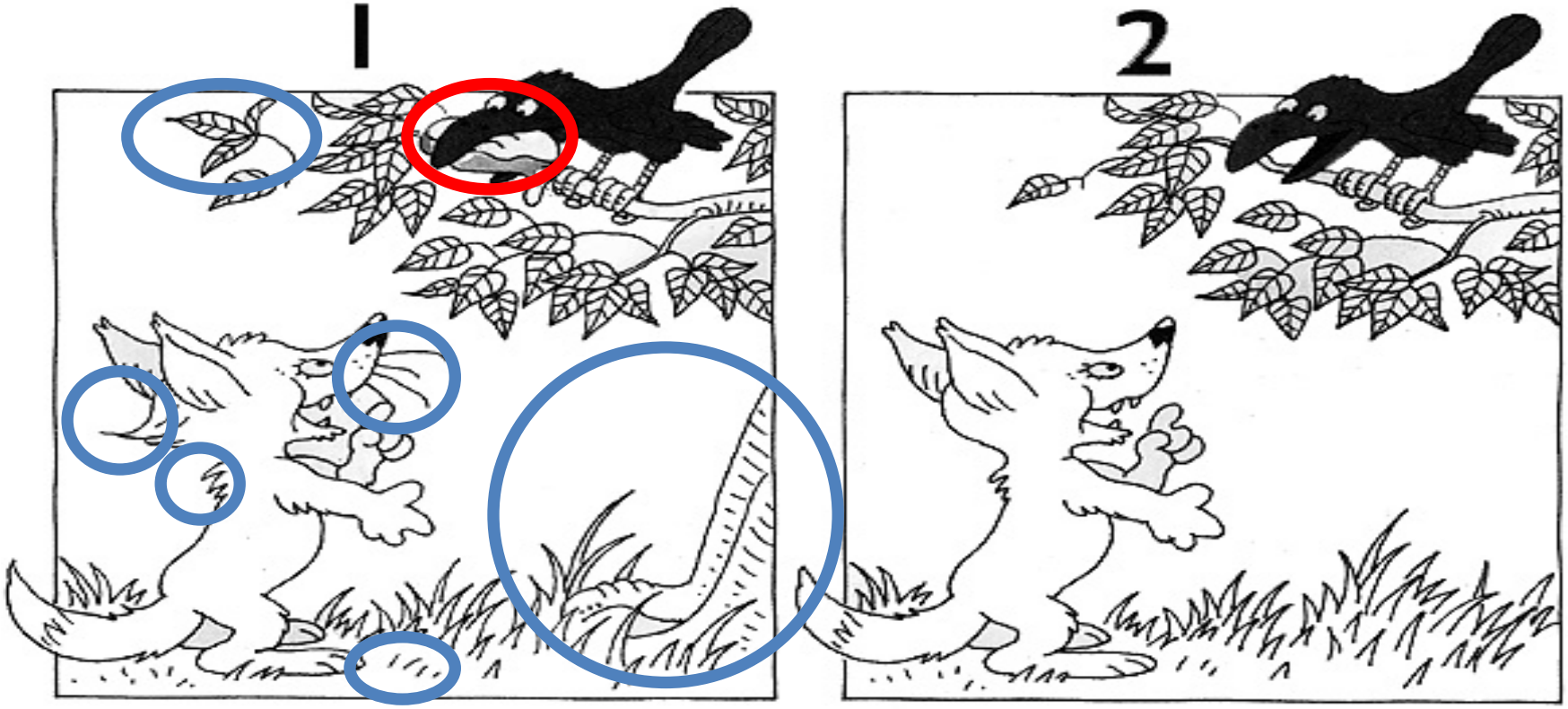
Commentary
Theme: Nanotechnology in Complex Drug Products: Learning from the Past, Preparing for the Future
Guest Editors: Katherine Tyner, Sau (Larry) Lee, and Marc Wolfgang
The AAPS Journal (© 2016)
DOI: 10.1208/s12248-016-9969-z

A Quality by Design Approach to Developing and Manufacturing Polymeric Nanoparticle Drug Products

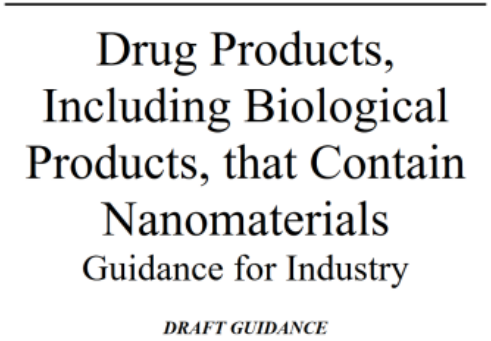
Greg Troiano,[1,2] Jim Nolan,[1] Donald Parsons,[1] Christina Van Geen Hoven,[1] and Stephen

Severity	Score	Description for Safety	Description for Efficacy	Uncertainty	
Negligible	2	No patient impact	No loss in efficacy	0	Impact established with clinical or *in vivo* data
Minor	4	Minor, reversible patient impact not requiring medical intervention	Minor loss in efficacy		
Moderate	6	Some impact on patient requiring medical intervention, reversible	Major loss in efficacy	2	Impact established *in vitro*
Major	8	Major, possibly irreversible impact on patient, not life threatening	Complete loss in efficacy	4	Hypothetical impact based on literature
Catastrophic	10	Life threatening illness or irreversible injury to patient	Negative efficacy (accelerates disease)	6	Unknown

The dilemma of the critical quality attributes



FDA's factors for assessment of nanomaterials


Drug Products, Including Biological Products, that Contain Nanomaterials
Guidance for Industry
DRAFT GUIDANCE

1. Adequacy of characterization of the material structure and its function
2. Complexity of the material structure
3. Understanding of the mechanism by which the physicochemical properties of the material impact its biological effects (eg effect of particle size on PK parameters)
4. Understanding the in vivo release mechanism based on the material physicochemical properties
5. Predictability of in vivo release based upon established in vitro release methods
6. Physical and chemical stability
7. Maturity of the nanotechnology (including manufacturing and analytical methods)
8. Potential impact of manufacturing changes, including in-process controls and the robustness of the control strategy on critical quality attributes of the drug product
9. Physical state of the material upon administration
10. Route of administration
11. Dissolution, bioavailability, distribution, biodegradation, accumulation and their predictability based on physicochemical parameters and animal studies

Manufacturing defines the product

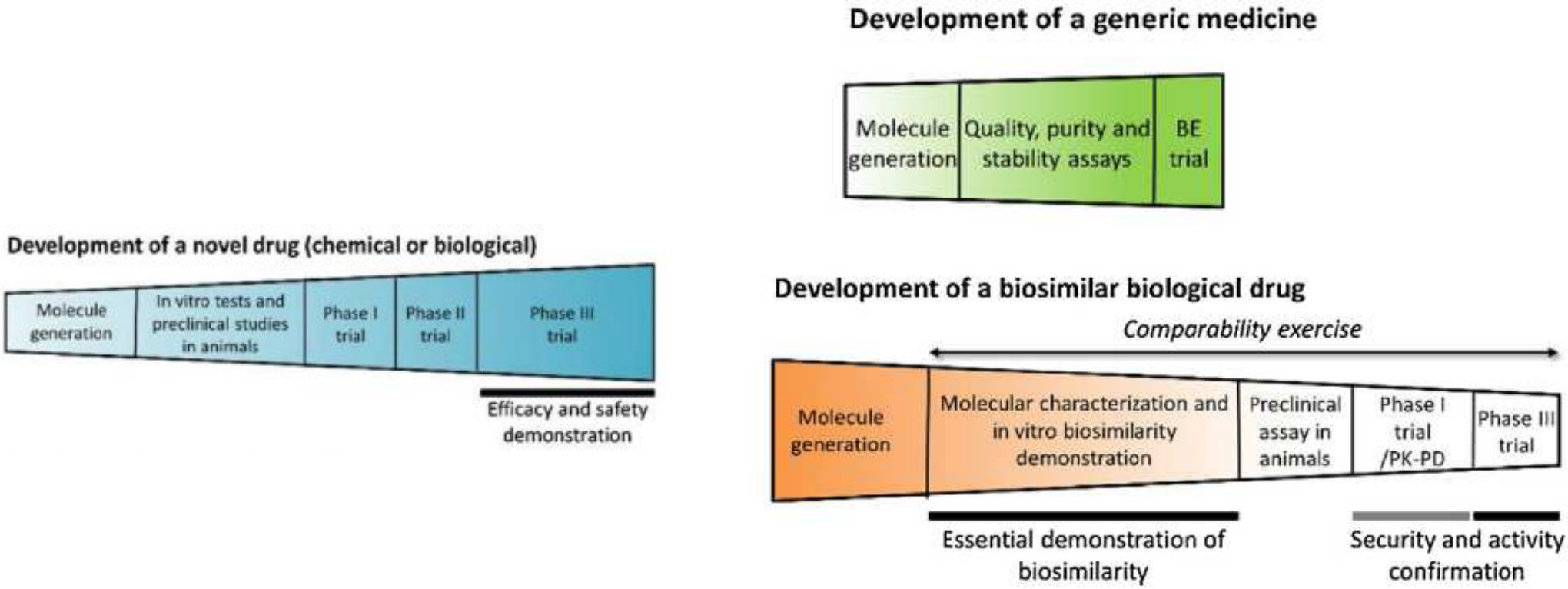
Drug Products, Including Biological Products, that Contain Nanomaterials

Guidance for Industry

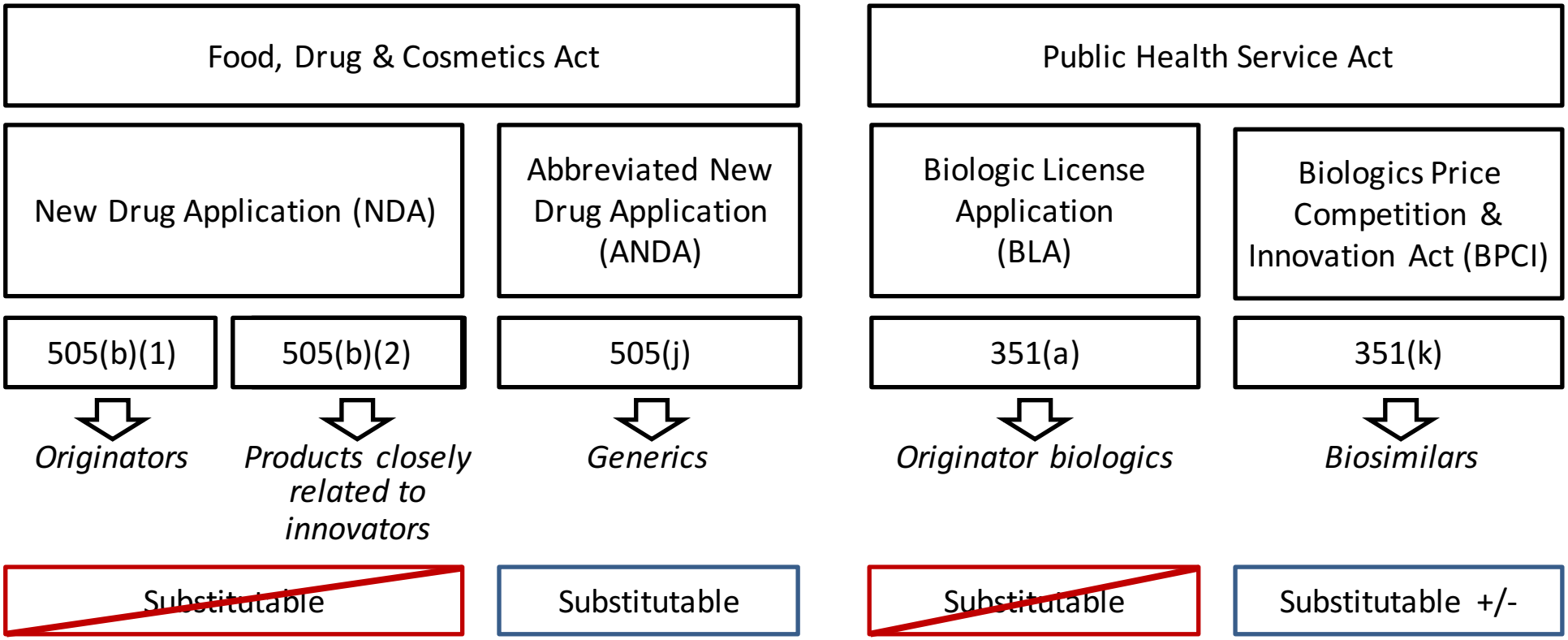
DRAFT GUIDANCE

Nanomaterials are engineered and manufactured to elicit novel product properties and clinical outcomes. The quality, safety, or efficacy of drug products containing nanomaterials can, however, be very sensitive to process conditions and production scales. Moreover, environmental controls should be established early in the development stage to prevent cross-contamination. This type of process and scale dependency, coupled with inherent polydispersity of some nanomaterials, makes it a priority to assess the risk to quality associated with the nanomaterial attributes, and develop adequate detectability of both nanomaterial and process failures at the development stage. As such, the earlier that CQAs can be identified during development, the more quickly in-process controls can be designed and implemented in the manufacturing process. A well-disciplined design control approach can generate key process knowledge, especially for those areas where, in the absence of comprehensive understanding, variability is not predictable, scale effects are unknown, and where results cannot be extrapolated or interpolated to demonstrate safety and efficacy.

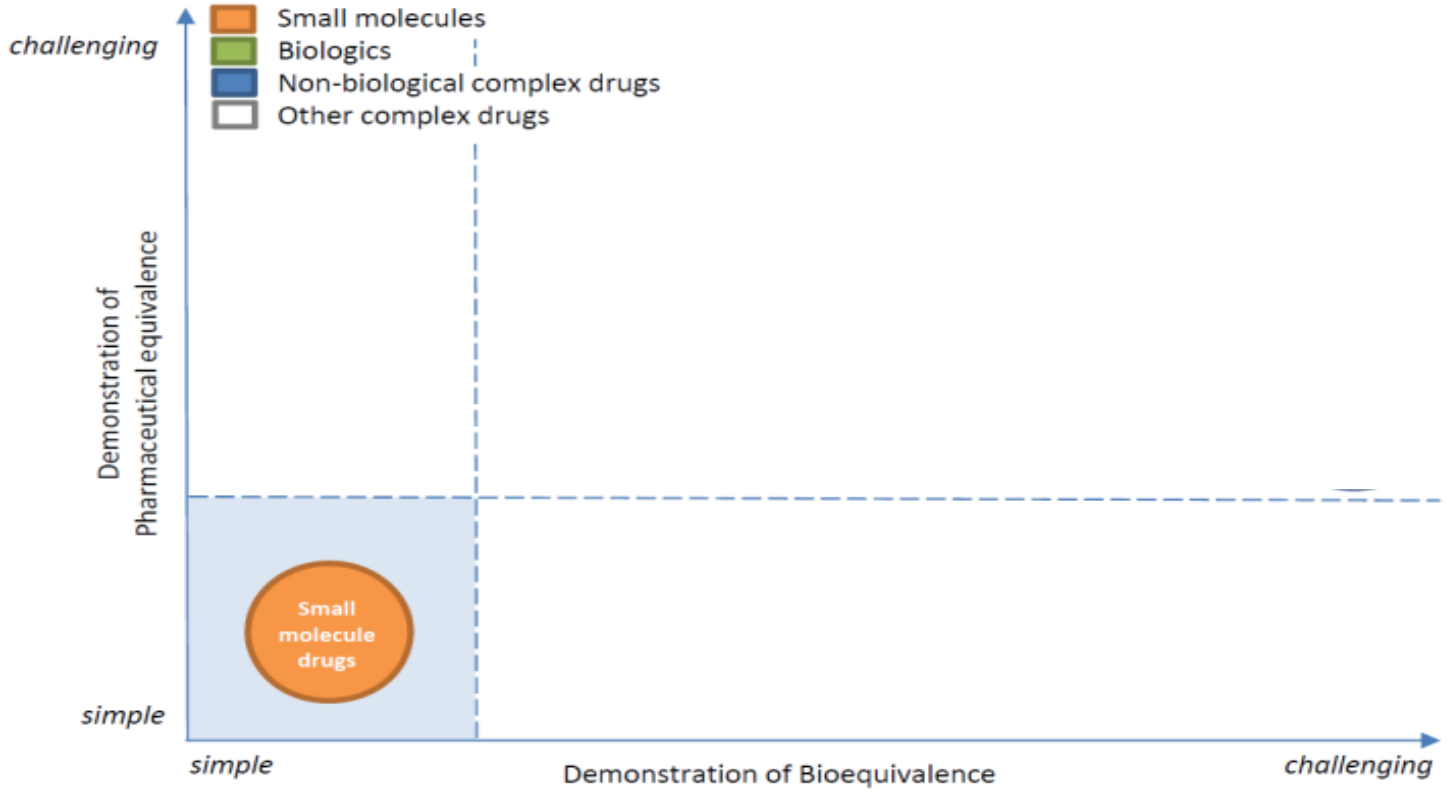
Regulatory Approach Links Physicochemical Characteristics to Clinical Outcome



FDA regulatory pathways

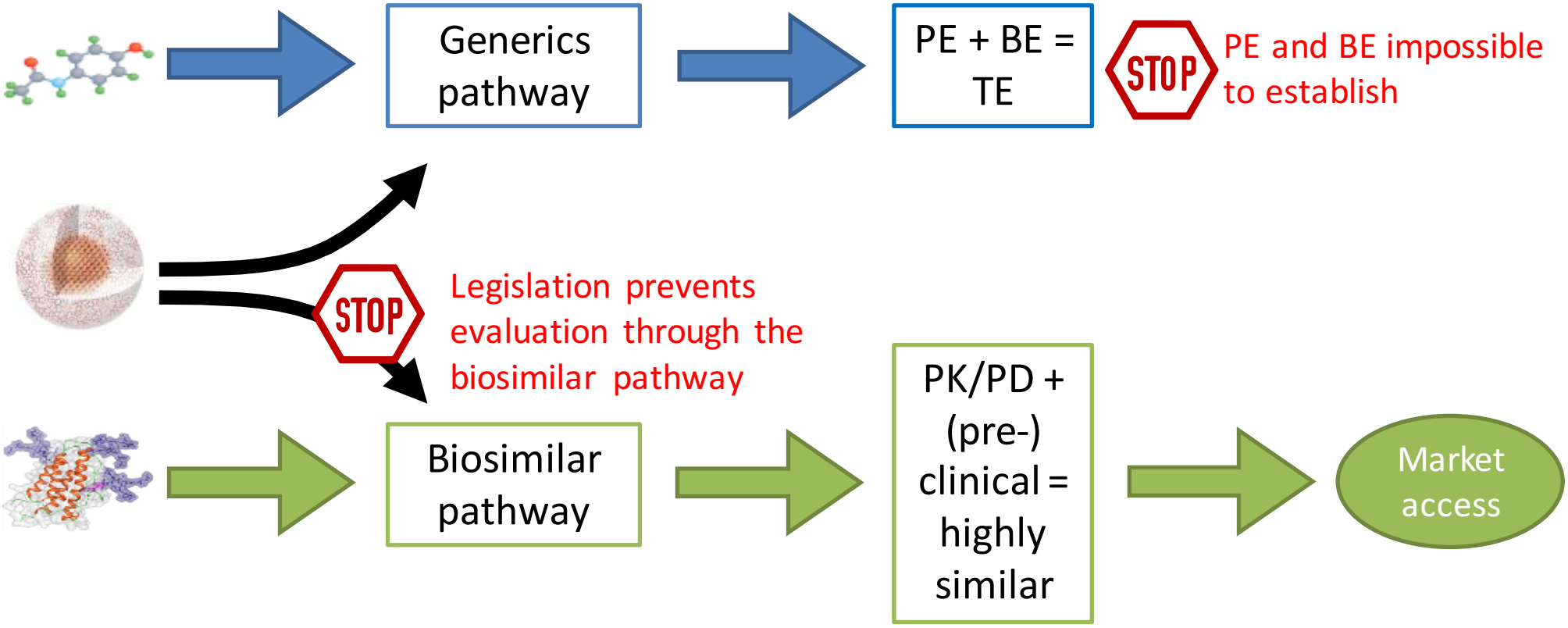


The PE + BE = TE challenge for complex drugs



Adapted from Hussaarts L *et al. Ann N Y Acad Sci* 2017;1407:39–49.

Current regulatory pathways are not suitable for NBCD approval



Authorities acknowledge the complexity: White Paper

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: Annals Reports
CONCISE ORIGINAL REPORT

Equivalence of complex drug products: advances in and challenges for current regulatory frameworks

Leonie Hussaarts,[1] Stefan Mühlebach,[2] Vinod P. Shah,[3] Scott McNeil,[4] Gerrit Borchard,[5] Beat Flühmann,[2] Vera Weinstein,[6] Sesha Neervannan,[7] Elwyn Griffiths,[8] Wenlei Jiang,[9] Elena Wolff-Holz,[10] Daan J.A. Crommelin,[11] and Jon S.B. de Vlieger[1]

Ill-defined regulatory pathways delay approvals …

VIFOR PHARMA

United States Government Accountability Office

GAO

Report to Congressional Requesters

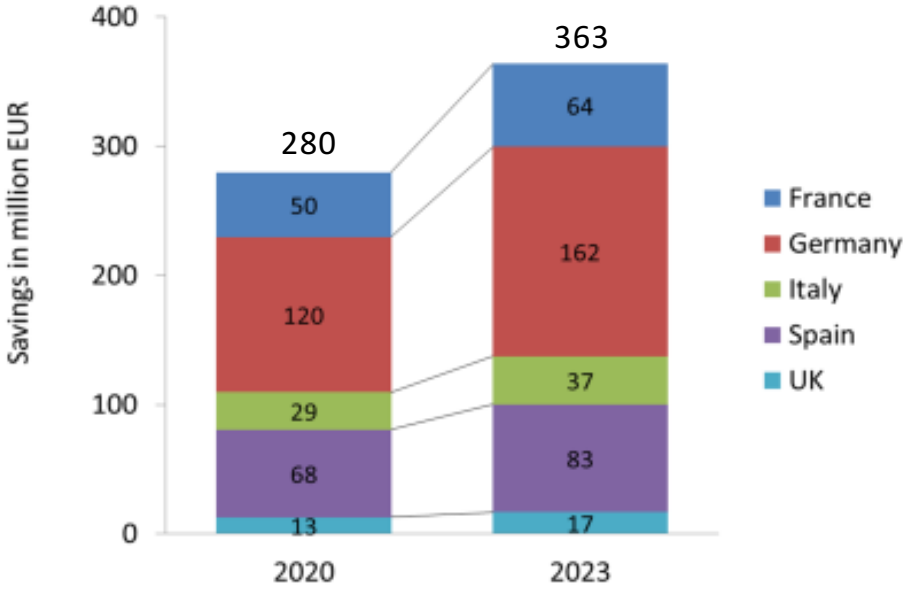
Drug name[a]	Submission of first approved generic application[b]	First generic approval	product-specific guidance issued
Doxorubicin hydrochloride (liposomal)	June 2011	February 2013	February 2010
Enoxaparin sodium injection	August 2005	July 2010	October 2011
Glatiramer acetate injection	December 2007	April 2015	April 2016
Propofol	March 1997	January 1999	June 2016
Sodium ferric gluconate complex in sucrose	March 2006	March 2011	June 2013

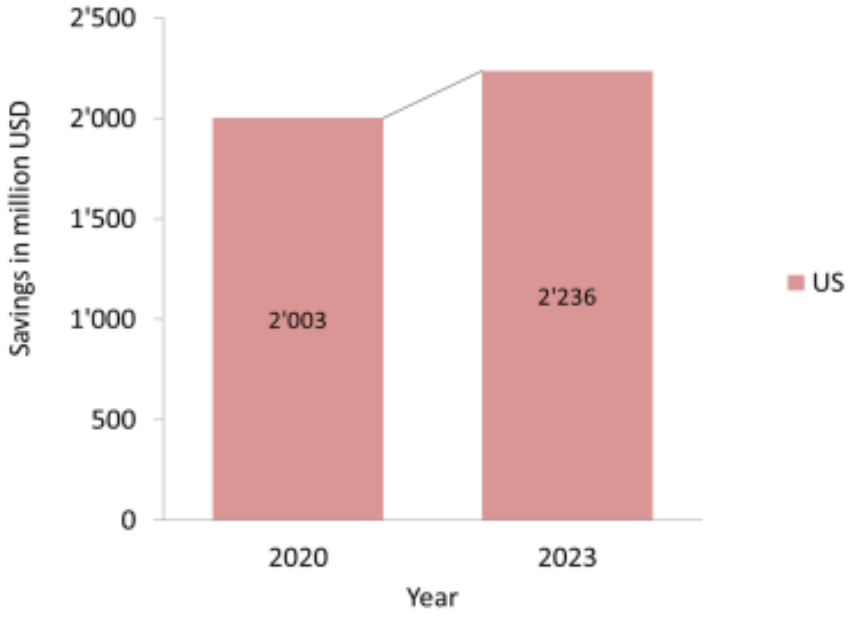
Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-18-80

[a]FDA approved a generic version of a sixth nonbiological complex drug—sevelamer carbonate—during fiscal year 2017.

[b]FDA may have received an application for a generic version prior to receiving the applications that were ultimately the first to be approved. However, as required by 21 C.F.R. § 314.430 (2016), FDA will not disclose the existence or other information concerning an unapproved application unless that information is publically disclosed by the sponsor.

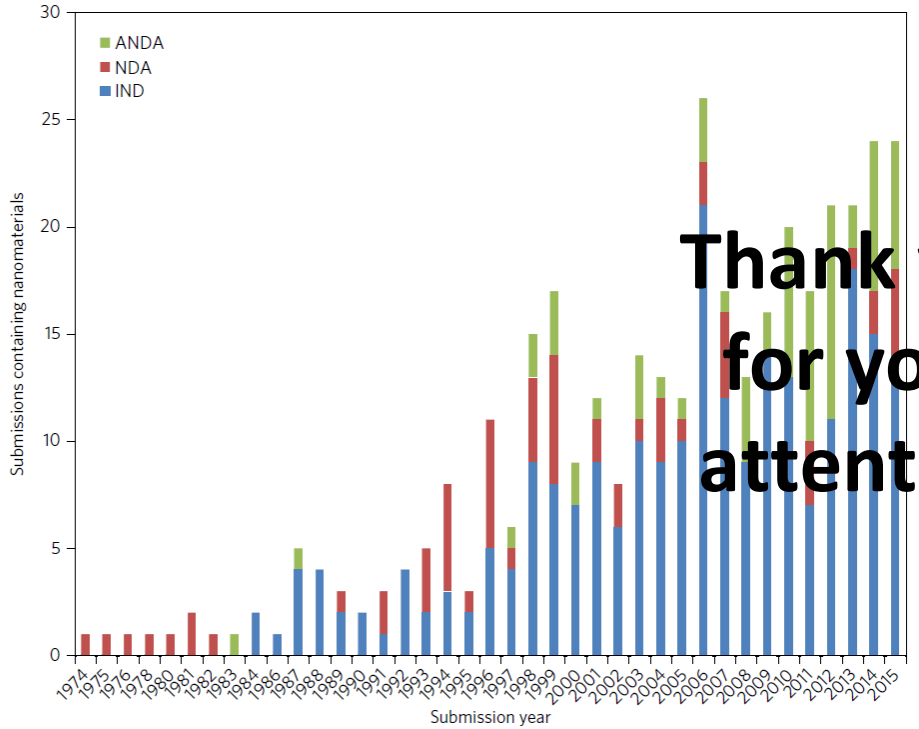
Ill-defined regulatory pathways delay approvals … and have significant financial impact





Adapted from Flühmann et al. EJPS 2018

Today, we see only the tip of the iceberg...



Thank you for your attention

Figure 1 | Number of nanomaterial product applications submitted to CDER by year. Applications are separated as INDs, NDAs and ANDAs.

INDs, investigational new drugs

D'Mello SR *et al. Nat Nanotechnol* 2017;12:523–9.