U.S. FOOD & DRUG ADMINISTRATION

Development and Characterization of Generic Drug Products Containing Nanomaterials

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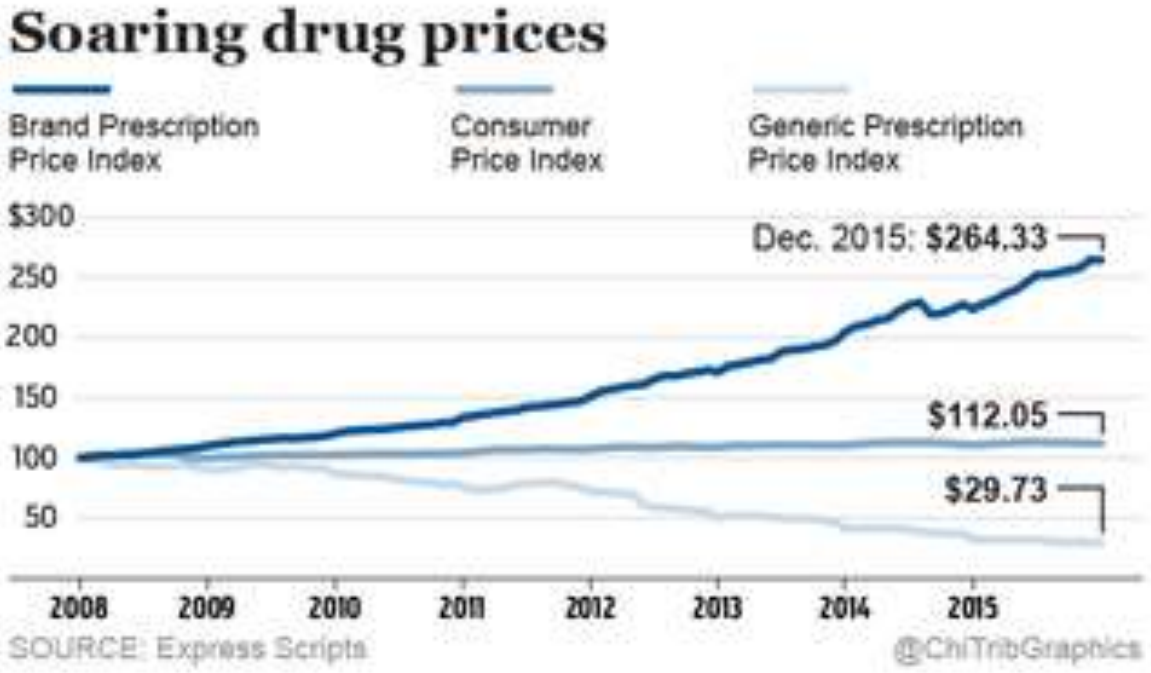
Development of Generic Drug Products Containing Nanomaterials

- What is a generic drug and the importance of physicochemical characterization of generic drugs containing nanomaterials
- Facilitating generic drug development via the Generic Drug User Fee Amendments (GDUFA) research program
- Examples of GDUFA research on advanced analytical methods for characterizing nanomaterial equivalence
- Examples of drugs containing nanomaterials and notable generic approvals

Impact of Generic Drugs

- Generics create competition that can reduce drug prices, saving the U.S. health care system $338 billion dollars in 2020 and improving patient access and adherence to a therapy.[1]
- Generics can reduce drug shortages by diversifying the supply chain.
- Ninety percent of prescriptions filled in the United States are for a generic, but many complex[2] drug products still do not have a generic available.



Chicago Tribune, 2016

1. Association for Accessible Medicines' 2021 Report: https://accessiblemeds.org/resources/reports/2021-savings-report ; and Ophthalmology 122.4 (2015): 738-747
2. Complex product as per FDA's 2016 GDUFA II Commitment Letter https://www.fda.gov/media/101052/download

NDA vs. ANDA Review Process

New Drug Application (NDA)

Brand Name Drug

NDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing

6. Animal Studies
7. Clinical Studies
8. Bioavailability

Abbreviated NDA (ANDA)

Generic Drug

ANDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing

6. Bioequivalence

Generic Drugs

- FDA approved generic drugs are **Therapeutically Equivalent (TE)** to a Reference Listed Drug (RLD)
- They can be substituted for the RLD (brand product)
- Generic and RLD have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

Generic Drugs: Therapeutic Equivalence

A generic product that is TE to the RLD product must be:

- Pharmaceutical Equivalent (PE)
  - Contain identical amount of the identical active ingredient(s)
  - Identical dosage form
  - Identical route of administration
  - Does not necessarily contain the same inactive ingredients *
  - Meet identical compendial or other applicable standards
- Bioequivalent (BE)
  - The absence of a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action when administered under similar conditions

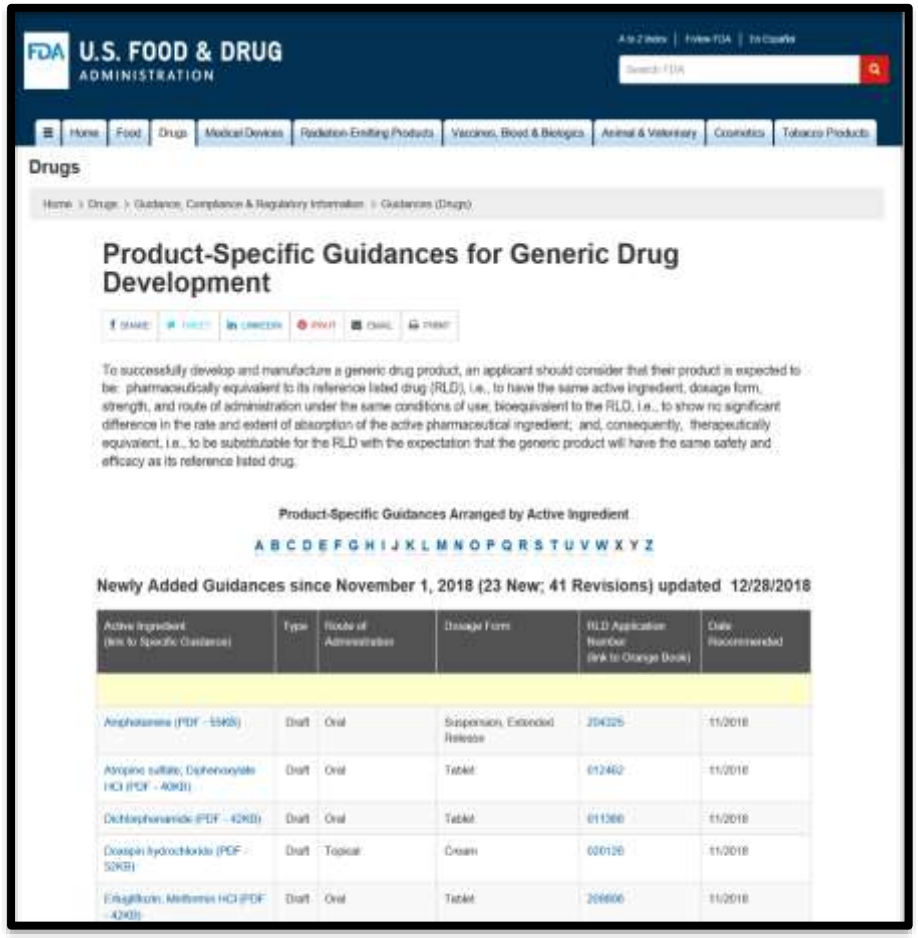
** If required under 21 CFR 314.94(a)(9) or recommended by a product specific guidance*

Common PE and BE Study Considerations for Generic Products Containing Nanomaterials

- Section VI.B of FDA's guidance for industry, *Drug Products, Including Biological Products, that Contain Nanomaterials* (April 2022), outlines considerations for generic product development:
  - Differences in the physicochemical properties of a nanomaterial-based product may influence the BE, pharmacology, and toxicology profiles. Therefore, sufficient scientific evidence is needed to demonstrate BE between a proposed generic drug and its nanomaterial-containing RLD.
    - For orally administered systemically acting drug products containing nanomaterials, comparative PK studies in blood/plasma are generally considered sufficient to demonstrate BE
    - For non-orally administered drug products, it is generally recommended that ***appropriate in vitro tests be part of demonstrating BE*** and in vivo BE studies when necessary
- Ultimately, given each product has unique properties and complexity, the information and types of studies that may be needed for generic approval are product specific.

Product-Specific Guidance

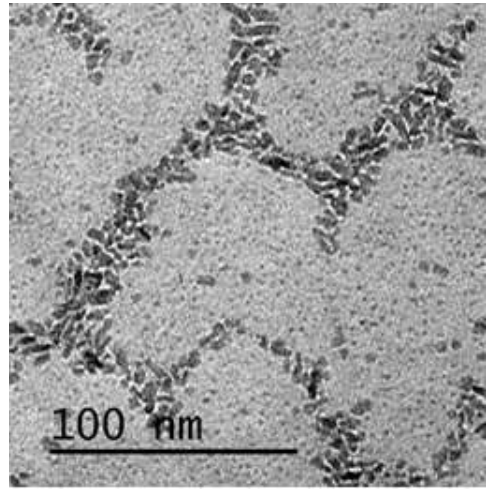
- Started in 2007, FDA's product-specific guidances[1] (PSGs) outline the information and types of studies recommended to support the approval of generic product referencing a specific RLD product.
  - PSGs are posted on a quarterly basis and as of Oct 2022, there are 2,032 posted PSGs.
    - 23 are for a complex ophthalmic or injectable product containing nanotechnology
  - ANDA applicants can propose an approach that deviates from FDA posted guidance but should include justification for the alternative approach including data (Module 2.7 and Module 5) and appropriate references.[2]



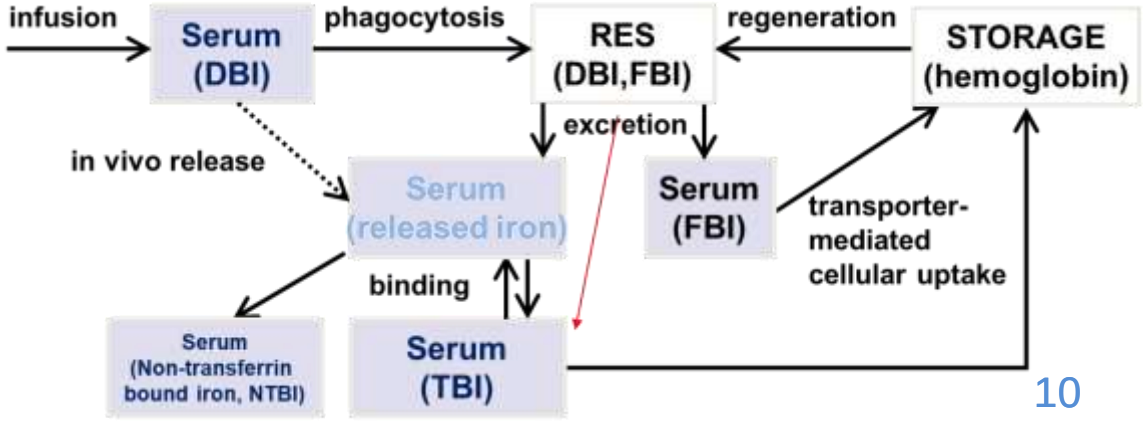
1. For the most recent version of the product-specific guidance, check the FDA product-specific guidance web page at: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
2. FDA's guidance for industry, *ANDA Submissions – Refuse-to-Receive Standards* (December 2016) https://www.fda.gov/media/86660/download

PSG on Ferric Oxyhydroxide (Injection)

- The PSG recommends:
  - A comparative in vivo PK study
    - **Measure of colloidal ferric oxyhydroxide in serum**, OR
    - Total iron in serum AND transferrin-bound iron in serum
  - Be formulated qualitatively (Q1) and quantitatively (Q2) the same as the RLD
  - Stoichiometric ratios/composition and Fe(II) content
  - Particle size distribution, evaluated using a Population Bioequivalence (PBE) statistical approach
  - **Particle morphology**
  - Electrical surface potential or charge
  - Crystalline structure
  - Magnetic properties
  - Fe(III) to Fe(II) reduction potential and reduction kinetics
  - Labile iron under multiple conditions

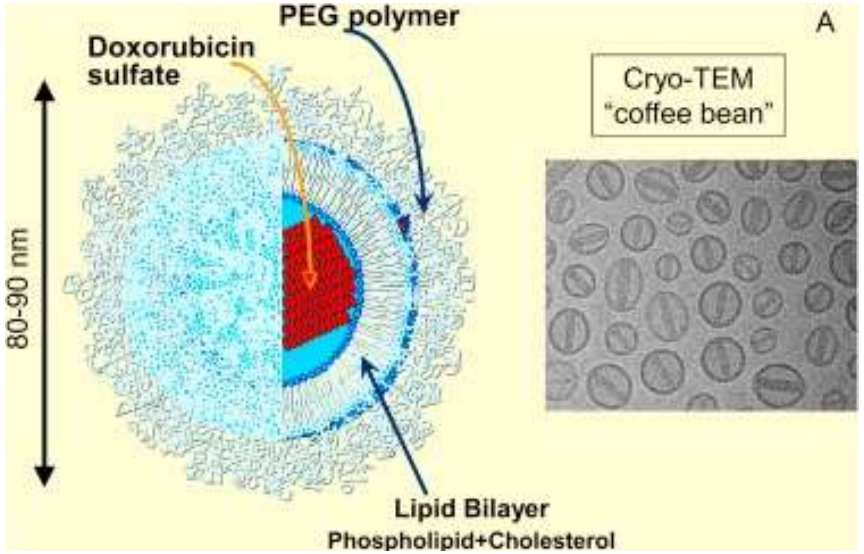


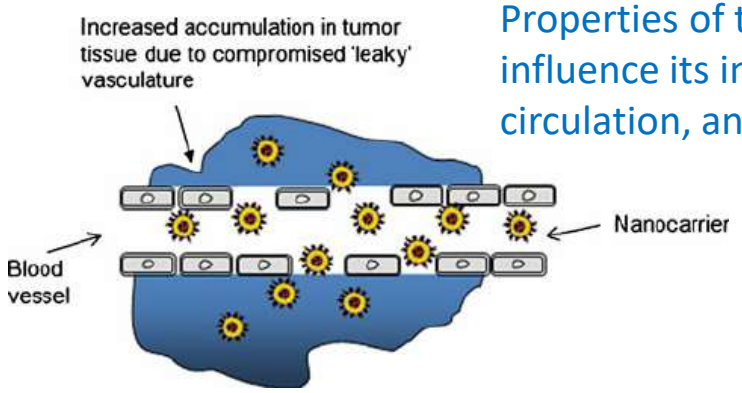
The body regulates available iron through a complex process that makes analytical measurement of infused iron levels challenging



PSG on Doxorubicin HCl (Liposomal) Injection

- In addition to a comparative in vivo PK study, the PSG also recommends a panel of comparative tests of critical quality attributes be conducted to support BE:
  - Be formulated qualitatively (Q1) and quantitatively (Q2) the same as the RLD
  - Liposome size distribution, evaluated using a Population Bioequivalence (PBE) statistical approach
  - Liposome composition
  - State of encapsulated drug
  - Internal environment
  - Lipid bilayer phase transitions
  - **Liposome morphology and number of lamellae**
  - Grafted PEG at the liposome surface
  - Electrical surface potential or charge
  - **In vitro leakage under multiple conditions**





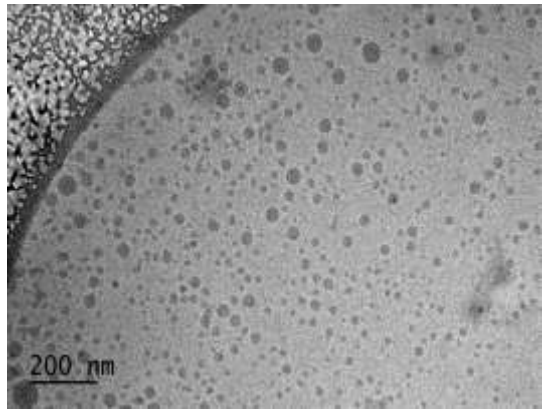
Properties of the liposome can influence its in vivo localization, circulation, and clearance

PSG on Cyclosporine Ophthalmic Emulsion

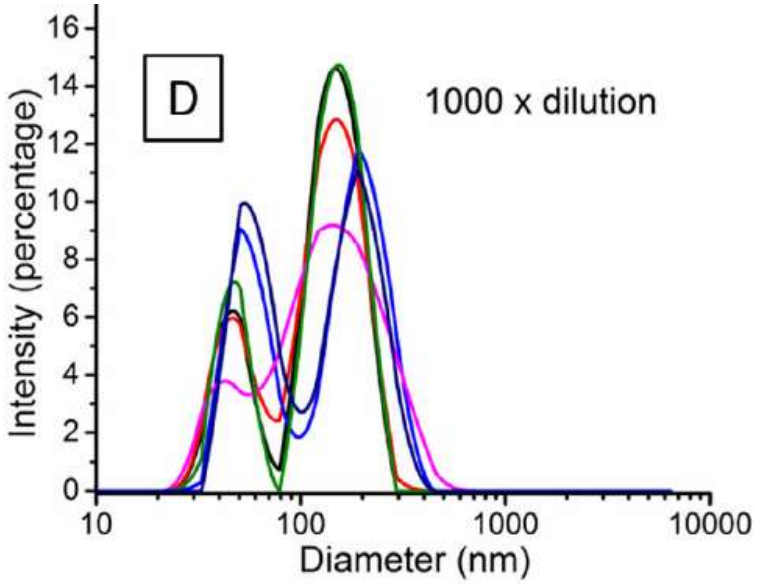
- The PSG recommends an in vitro option:
  - Be formulated qualitatively (Q1) and quantitatively (Q2) the same as the RLD
  - **Globule size distribution**, evaluated using an appropriate **histogram comparator** and PBE statistical approach
  - Electrical surface potential or charge
  - Viscosity, pH, drug distribution, and surface tension
  - In vitro drug release test

OR

- An in vivo option:
  - Comparative clinical endpoint study in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca



Formulation factors give rise to a polydisperse globule size measurement



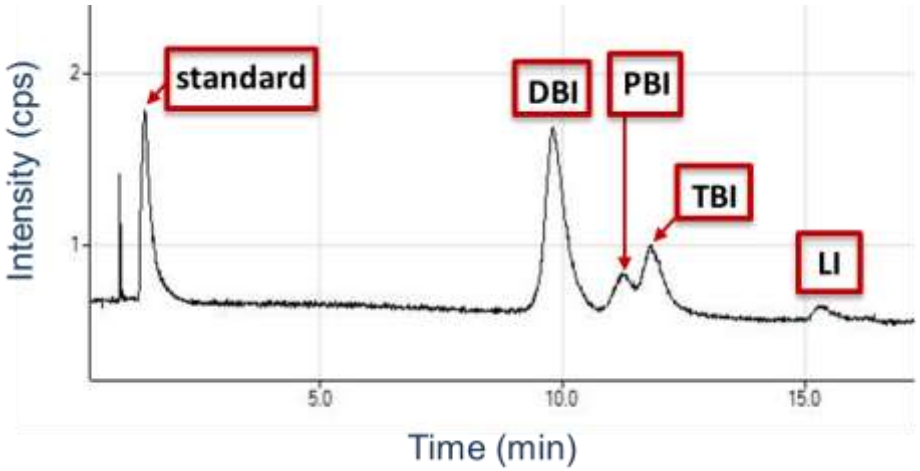
Petrochenko, Peter E., et al. International Journal of Pharmaceutics 550.1-2 (2018): 229-239.

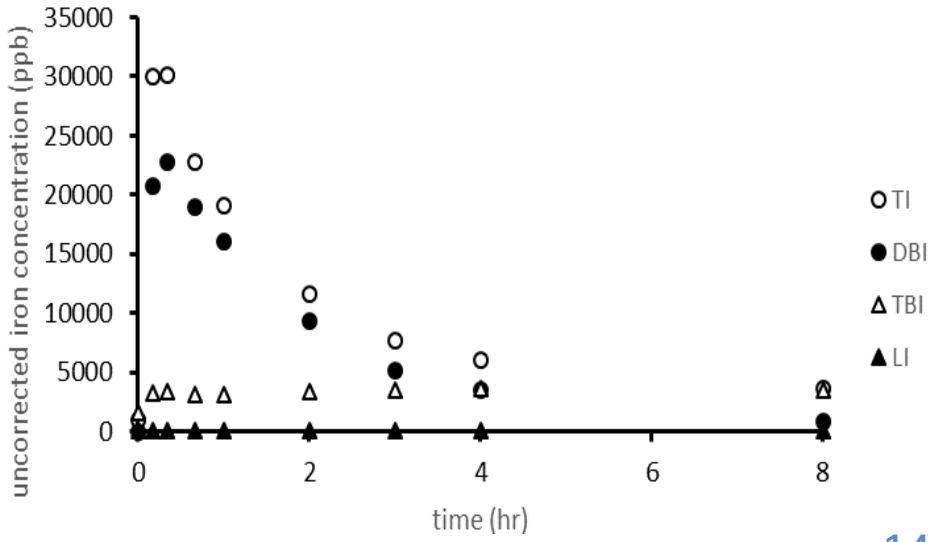
Generic Drug User Fee Amendments (GDUFA) Research

- FDA's research on complex generics helps the development of more generic competition in areas where bioequivalence evaluation is scientifically challenging
- FDA's research helps to make generic drug development and review more efficient
- In 2020, FDA's GDUFA Science and Research Program funded approximately $20 million in research

New Tools for Measuring Nanomaterial Analytes

- A new liquid chromatography–inductively coupled plasma–mass spectrometry (LC–ICP–MS) method was developed to accurately measure colloidal ferric oxyhydroxide drug (DBI) as well as the speciation of released iron: labile (LI), transferrin-bound (TBI), and protein [e.g., albumin and ferritin] bound (PBI), in plasma.
  - The direct measurement of DBI overcomes limitations of previous methods that necessitated measuring both Total iron and TBI and a parallel study design.

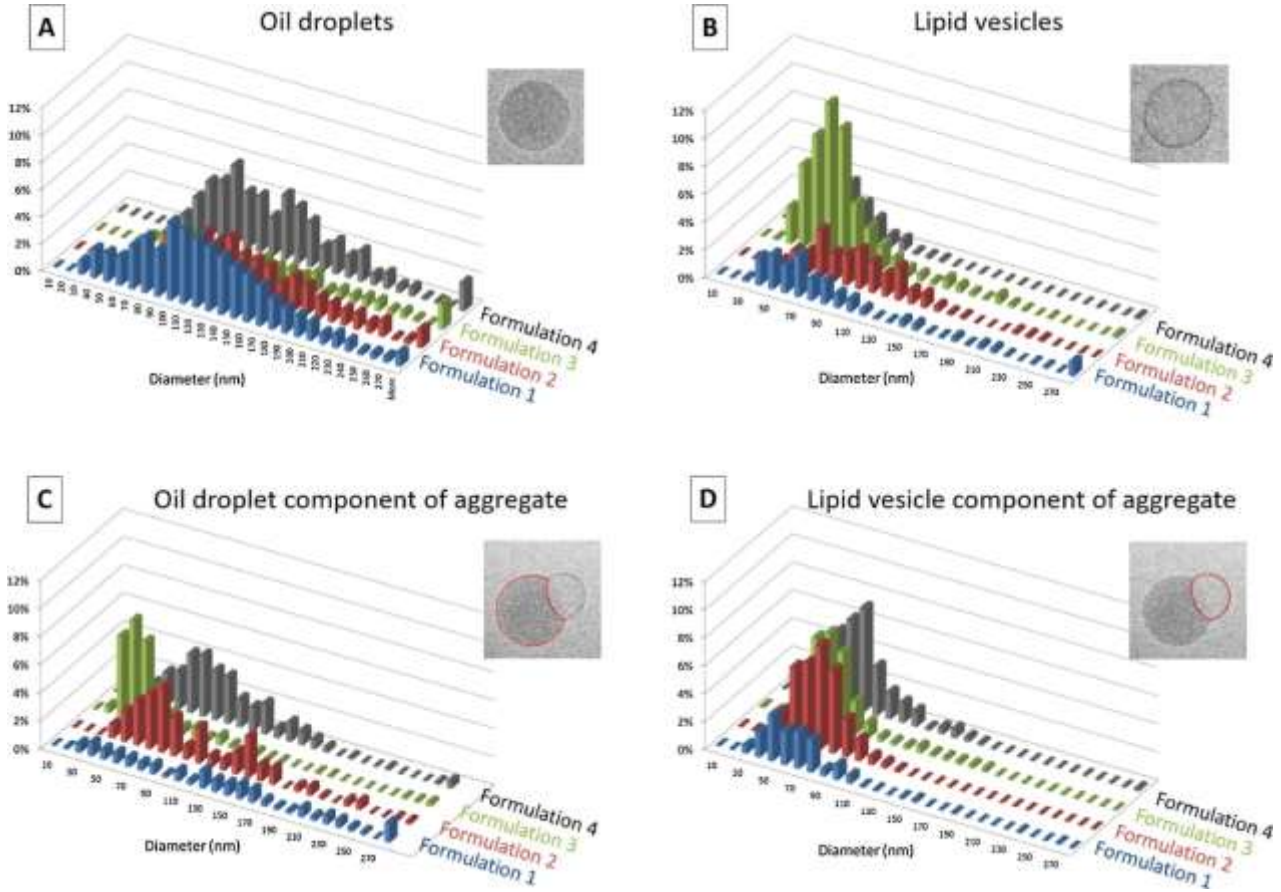


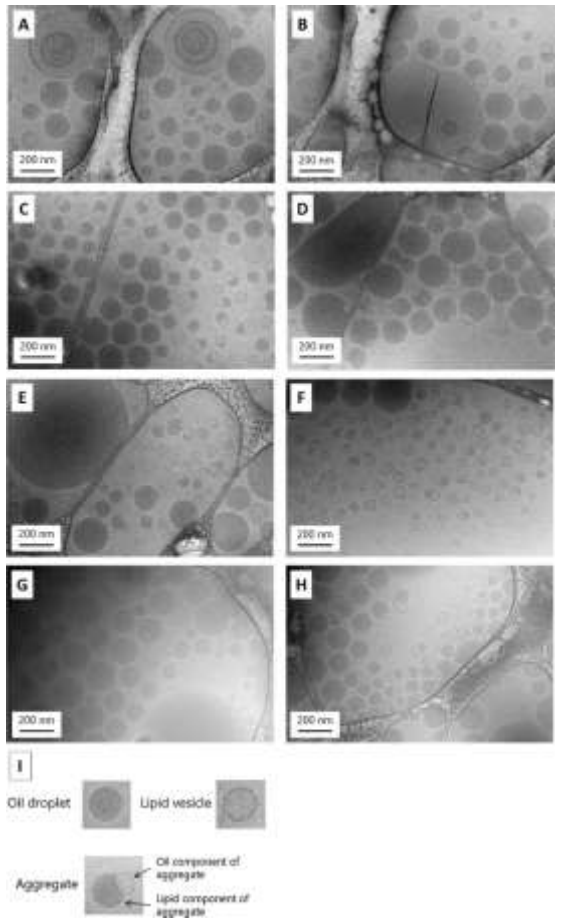


Neu, Heather M., et al. "Molecular pharmaceutics 16.3 (2019): 1272-1281.

Tools to Characterize Nanomaterial Structure

Cryo-Scanning Electron Microscopy combined with imaging software can compare the morphology and structural distribution of nanomaterials within the drug product



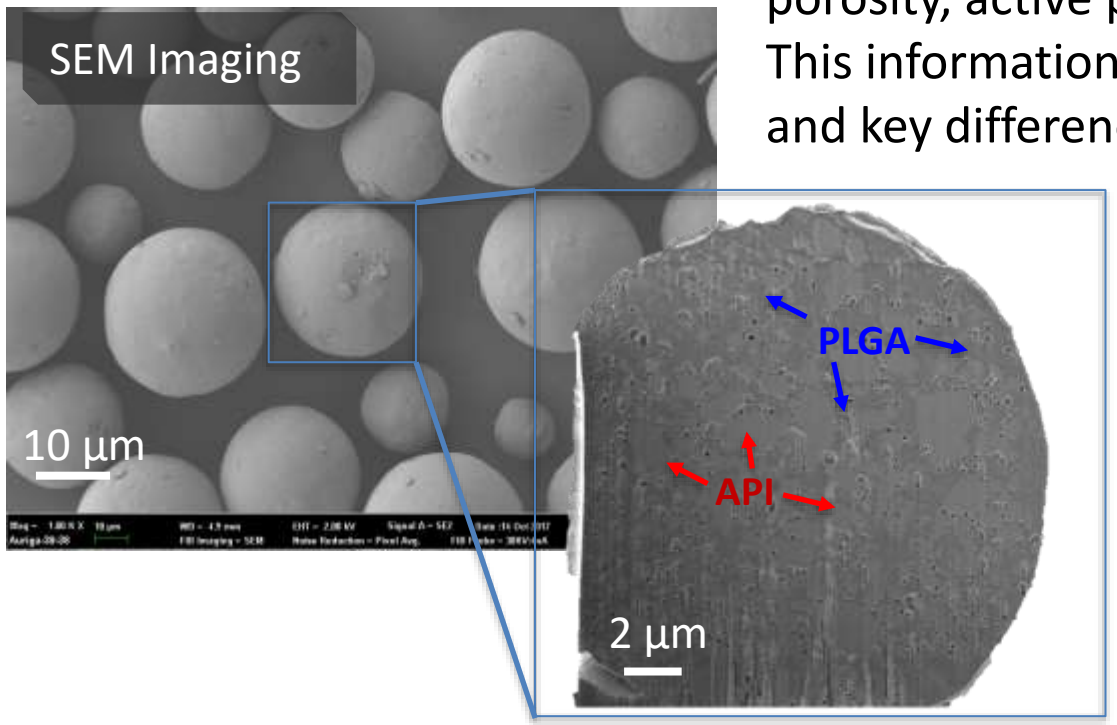


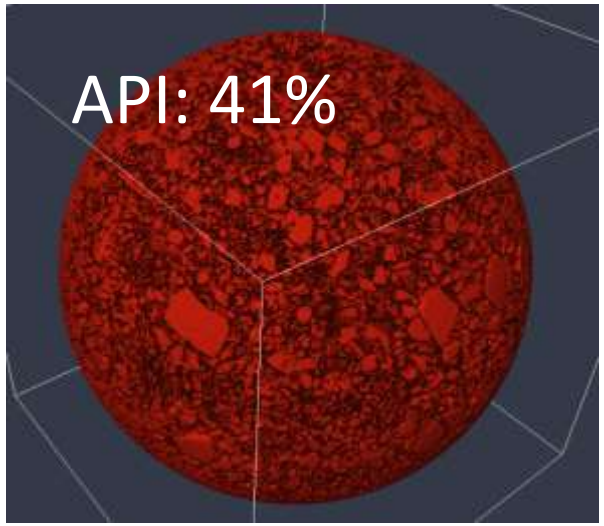
Wu, Yong, et al. *International Journal of Pharmaceutics* 577 (2020): 118998.

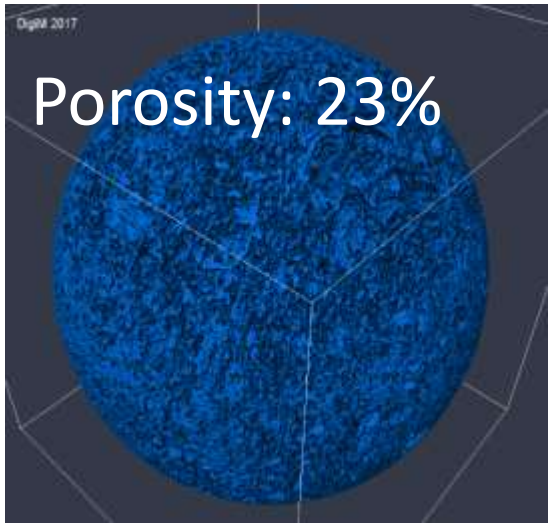
Focused Ion Beam Scanning Electron Microscopy (FIB-SEM)

FIB-SEM Cross Section of PLGA Controlled Release Microspheres

Artificial intelligence (AI)-based analyses of the imaging data can reconstruct porosity, active pharmaceutical ingredients (API), and PLGA polymer domains. This information could be helpful to better understand drug release behaviors and key differences in these domains that can impact BE.



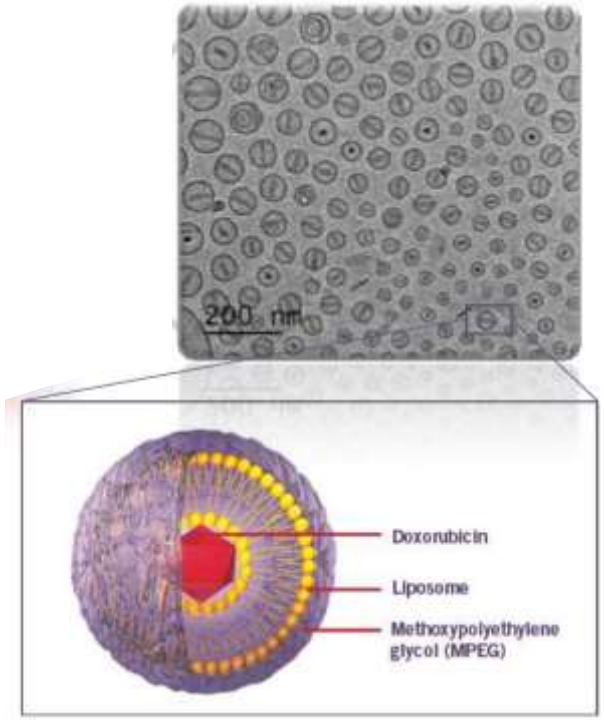


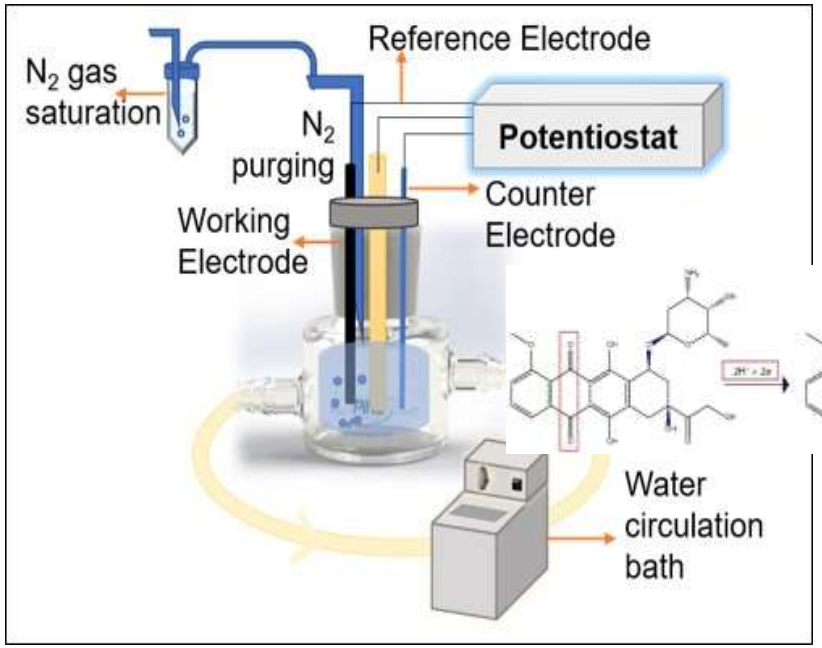


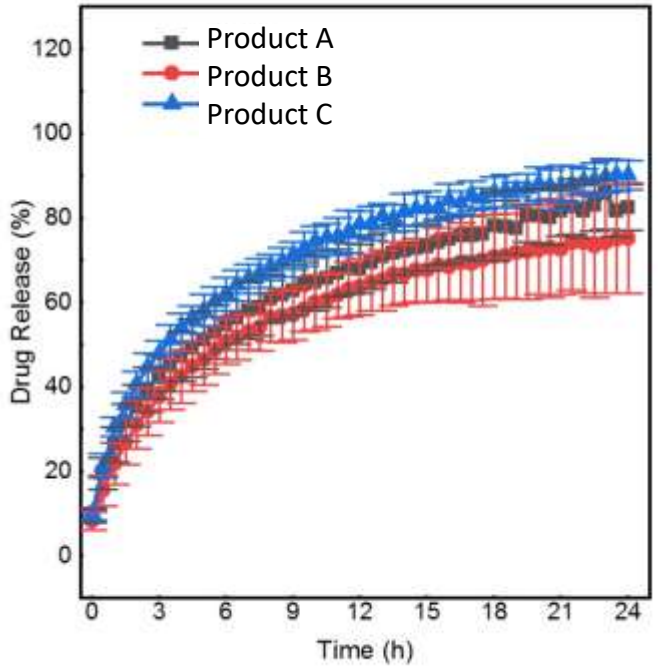
GDUFA Contract # 75F40119C10157 to DigiM Soluton LLC

New Tools for Measuring Drug Release from Products Containing Nanomaterials

- An electroanalytical method was developed for the continuous and direct quantitation of drug released from liposomes that overcomes the limitations and inaccuracies of conventional separation analysis methods.



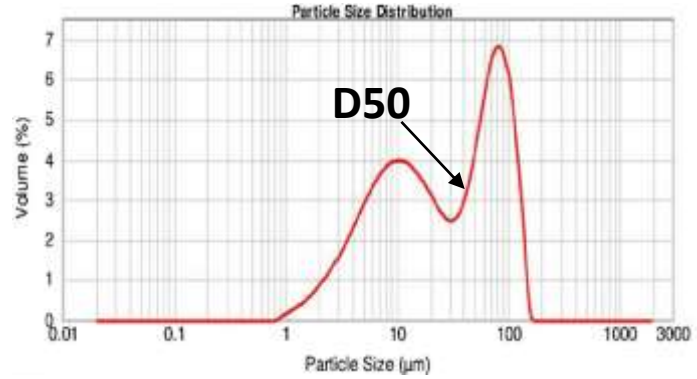


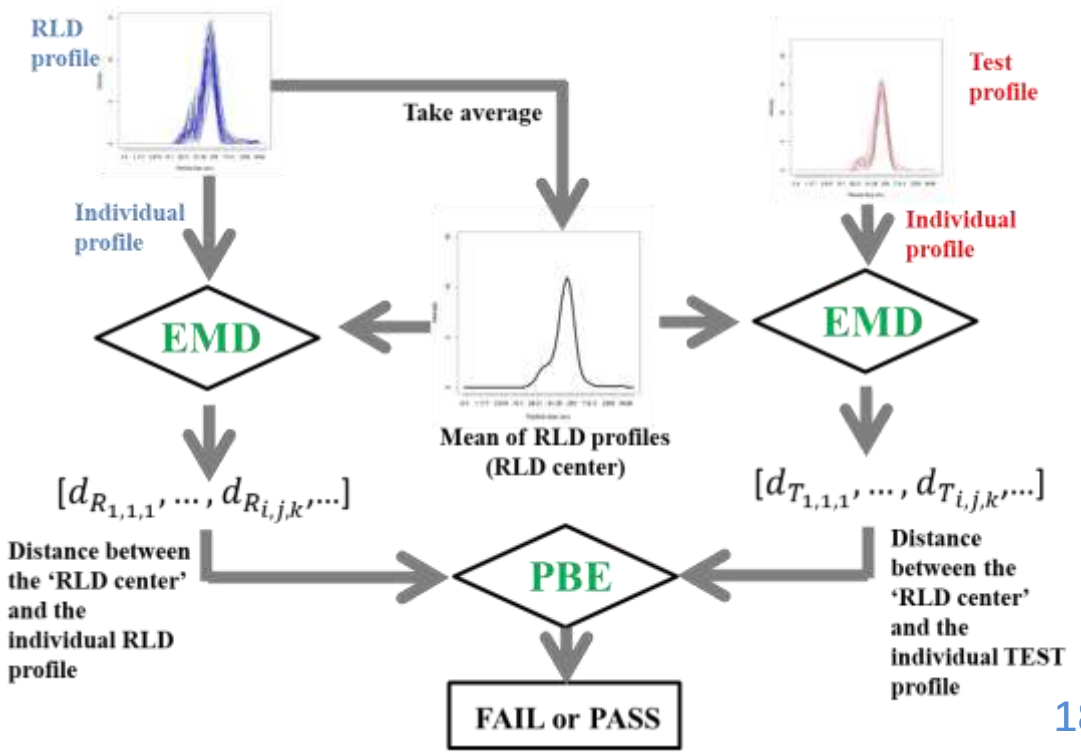


FDA GDUFA research project by Fatma M. Yurtsever, Dumindika A. Siriwardane, Wenlei Jiang, and Thilak Mudalige done at the Nanotechnology Core Facility (NanoCore) located on the U.S. Food and Drug Administration's Jefferson Laboratories campus (Jefferson, AR)

New Methods to Assess Equivalence of Nanomaterial Distribution

- A new Earth Mover Distance (EMD) approach was developed to describe the relative differences between two histograms. EMD overcomes limitations of D50 and SPAN descriptors for non-monomodal histograms.
  - When combined with PBE statistical assessment, EMD can enable comparison of any shape histograms, such as the multimodal globule size distribution of cyclosporine ophthalmic emulsions.





Hu, Meng, et al. The AAPS Journal 20.3 (2018): 1-10.

Notable Approvals of Generic Products Containing Nanomaterials

RLD (NDA #)	Brand Name	RLD Approval	Generic	ANDA #		Approval Date	
050718	Doxil	11/17/1995	Doxorubicin HCl liposomal injection	203263 212299	208657 207228	02/04/2013 09/10/2020	05/15/2017 10/12/2021
050740	AmBisome	08/11/1997	Amphotericin B liposomal injection	212514		12/14/2021	
022212	Durezol	06/23/2008	Difluprednate ophthalmic emulsion	211776 211526		08/09/2021 11/17/2021	
205894	Restasis	12/23/2002	Cyclosporine ophthalmic emulsion	205894		02/02/2022	
019627	Diprivan	10/02/1989	Propofol injectable emulsion	075102 074848 077908 206408	205307 205067 205576	01/04/1999 04/19/2005 03/17/2006 10/12/2021	12/22/2015 11/15/2018 09/16/2020
020955	Ferrlecit	02/18/1999	Ferric Oxyhydroxide injection	078215		03/31/2011	
022180	Feraheme	06/30/2009	Ferumoxytol intravenous	206604		01/15/2021	

Conclusions

- A generic product must demonstrate it is both pharmaceutically equivalent (PE) and bioequivalent (BE) to be designated therapeutically equivalent (TE) to the reference listed drug (RLD), i.e., the 'brand-name' product.
- FDA's guidance for industry, *Drug Products, Including Biological Products, that Contain Nanomaterials* (April 2022) and Product-Specific Guidances (PSGs) outline the information and types of studies recommended to develop a generic product containing nanomaterials.
- FDA is committed to supporting the latest scientific methods and tools to develop and evaluate generic products. GDUFA provides funding to conduct research that facilitates generic drug development and approval.
- The number of approved generic products containing nanomaterials has steadily increased. In 2021-2022 the first generic amphotericin B liposomal injection, difluprednate ophthalmic emulsion, ferumoxytol intravenous, and cyclosporine ophthalmic emulsion were approved.

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- Ying Zhang
- Yixuan Dong
- Haiou Qu

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- Thilak Mudalige (ORA)
- Fatma Yurtsever (ORA)
- Dumindika Siriwardane (ORA)
- Siyam M. Ansar (ORA)

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- National Institute for Pharmaceutical Technology and Education


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