Complex Generics Containing Nanomaterials: What's Next in the Pipeline?

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Outline

- Generic drugs and complex generics containing nanomaterials
- U.S. FDA approved NDAs and ANDAs containing nanomaterials
- Guidance development for nanomaterials
- Regulatory challenge and research opportunities for complex nanomaterials
- Global regulatory efforts to facilitate development of complex nanomaterials

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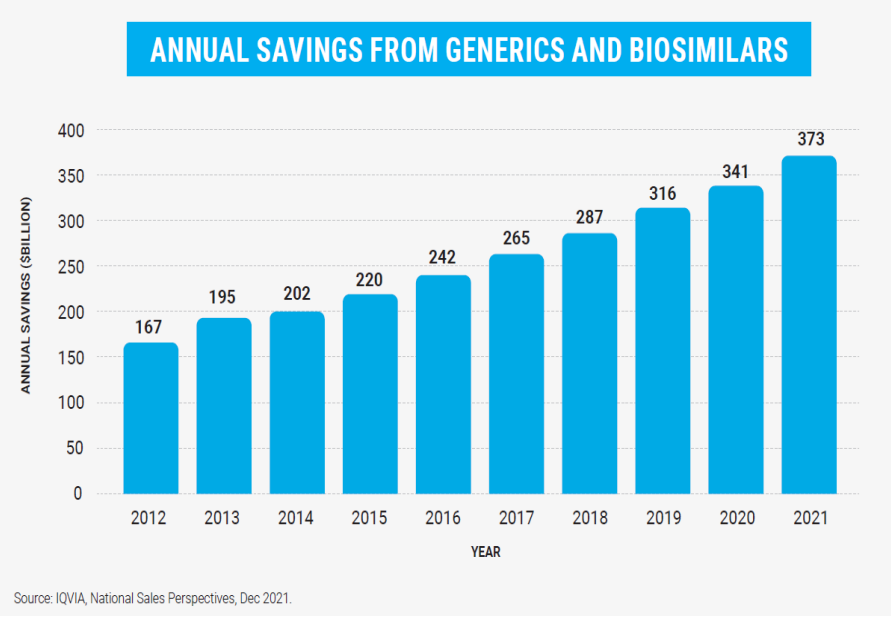
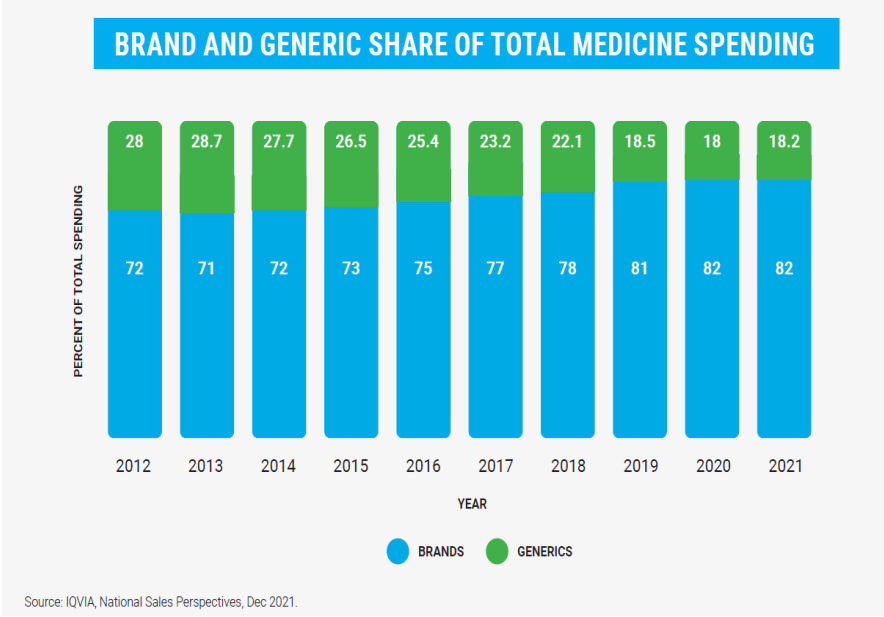
Generic Drugs and Complex Products

Generic Drugs

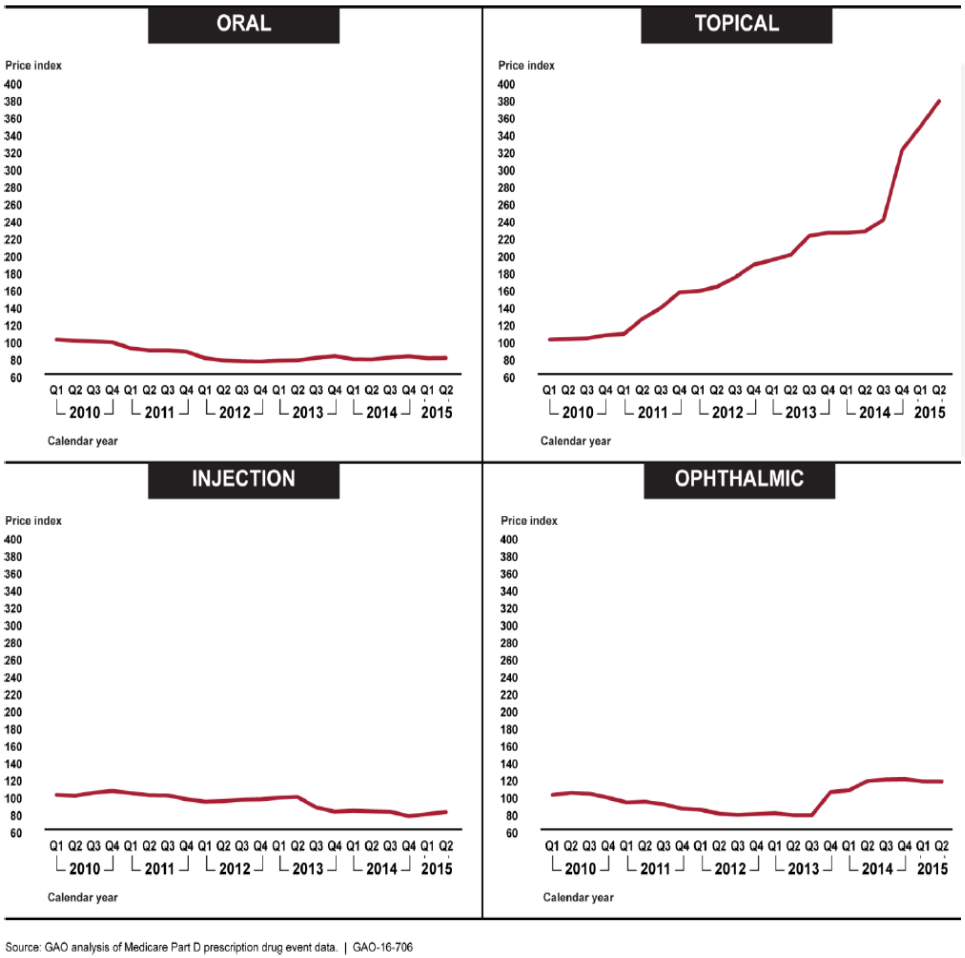
- Generic drugs are duplicates of reference listed drugs (RLDs)
- Same active ingredient, conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and bioequivalent to RLD





https://accessiblemeds.org/sites/default/files/2022-09/AAM-2022-Generic-Biosimilar-Medicines-Savings-Report.pdf

Products with Limited Generic Availability

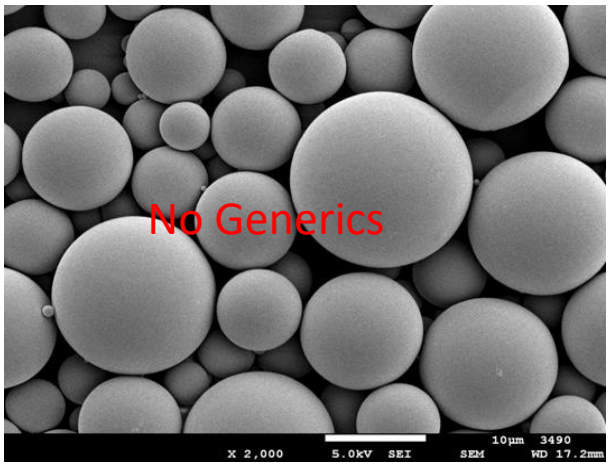


Source: GAO analysis of Medicare Part D prescription drug event data. | GAO-16-706

The GAO Report (GAO-16-706)

Orally inhaled drug products

Poly-(lactic-co-glycolic acid) (PLGA) microspheres



Complex Products

According to the **GDUFA II** and **III commitment letter**, complex products generally include products with

1) complex active pharmaceutical ingredients (APIs);
2) complex formulations;
3) complex routes of delivery;
4) complex dosage forms;
5) complex drug-device combination;
6) other products where there is complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.

GDUFA: Generic Drug User Fee Amendments

https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf
https://www.fda.gov/media/153631/download

Complex active pharmaceutical ingredients (APIs)	• Any drug product containing a complex API, regardless of administration routes and dosage forms e.g., Conjugated Estrogen Tablet, Glatiramer Acetate Injection
Complex routes of delivery	• Any non-solution drug product with a non-systemic site of action (e.g., topical, ophthalmic, local gastrointestinal (GI) action) e.g., Cyclosporine Emulsion, Acyclovir Cream
Complex dosage forms/ formulations	• Any non-oral complex formulation/dosage form product where there are often two or more discrete states of matter within the formulation e.g., Doxorubicin HCl Liposomes, Leuprolide Acetate for Depot Suspension
Complex drug-device combinations	• Where the drug constituent part is pre-loaded in a product-specific device constituent part or is specifically cross-labeled for use with a specific device, in which the device design affects drug delivery to the site of action and/or absorption e.g., Epinephrine Injection (autoinjector)
Other products	• Any solid oral opioid drug products with FDA approved labeling for that show properties (and thus gaining their labeling) to meaningfully deter drug abuse e.g., Hydrocodone Bitartrate ER Tablet

CDER Manual of Policies & Procedures | MAPP | FDA MAPP 5240.10 Classifying Approved New Drug Products and Drug-device Combination Products as Complex Products for Generic Drug Development Purposes

Complex Dosage Forms/Formulations

Semisolid Dosage Forms

- Creams, lotions, gels, ointment, and foams

Non-oral Nanotechnology Products

- Nano size liposome formulations (e.g., doxorubicin)
- Iron complex formulations (e.g., sodium ferric gluconate)
- Nano-suspension (e.g., paclitaxel)
- Self-assembling nanotubes (e.g., lanreotide acetate)
- Nano-emulsions (e.g., cyclosporine, difluprednate)
- Lipid complex drugs (e.g., amphotericin B lipid complex)

→ **Complex Products Containing Nanomaterials**

Long-Acting Injectable (LAI) Products

- Suspensions (e.g., aripiprazole LAI suspension)
- Multivesicular liposomes (e.g., bupivacaine liposomes)
- Biodegradable implants/inserts (e.g., leuprolide acetate)
- Microspheres (e.g., risperidone)

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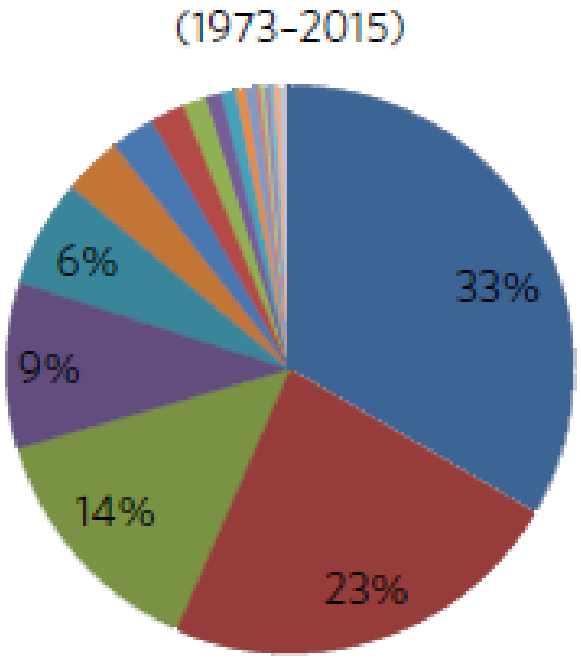
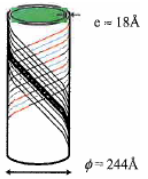
Products Containing Complex Nanomaterials in United States

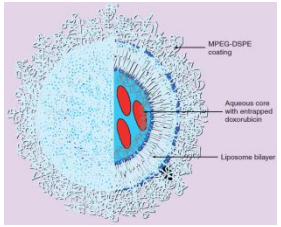
Submissions to the U.S. FDA of Drug Products Containing Nanomaterials

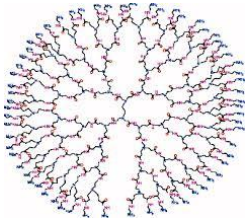
- Liposome
- Nanocrystal
- Emulsion
- Iron-polymer complex
- Micelle
- Drug-protein complex
- Drug-polymer complex
- Dendrimer
- Polymeric NP
- Nanobubble
- Silica NP
- Drug-lipid complex
- Drug-metal complex
- Protein NP
- Drug NP
- Solid lipid NP
- Nanotube
- Metal-protein complex
- Metal-nonmetal complex
- Metal-polymer complex

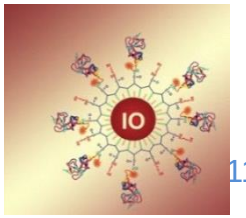


D'Mello S. et al. Nature Nanotechnology DOI: 10.1038/NNANO.2017.67

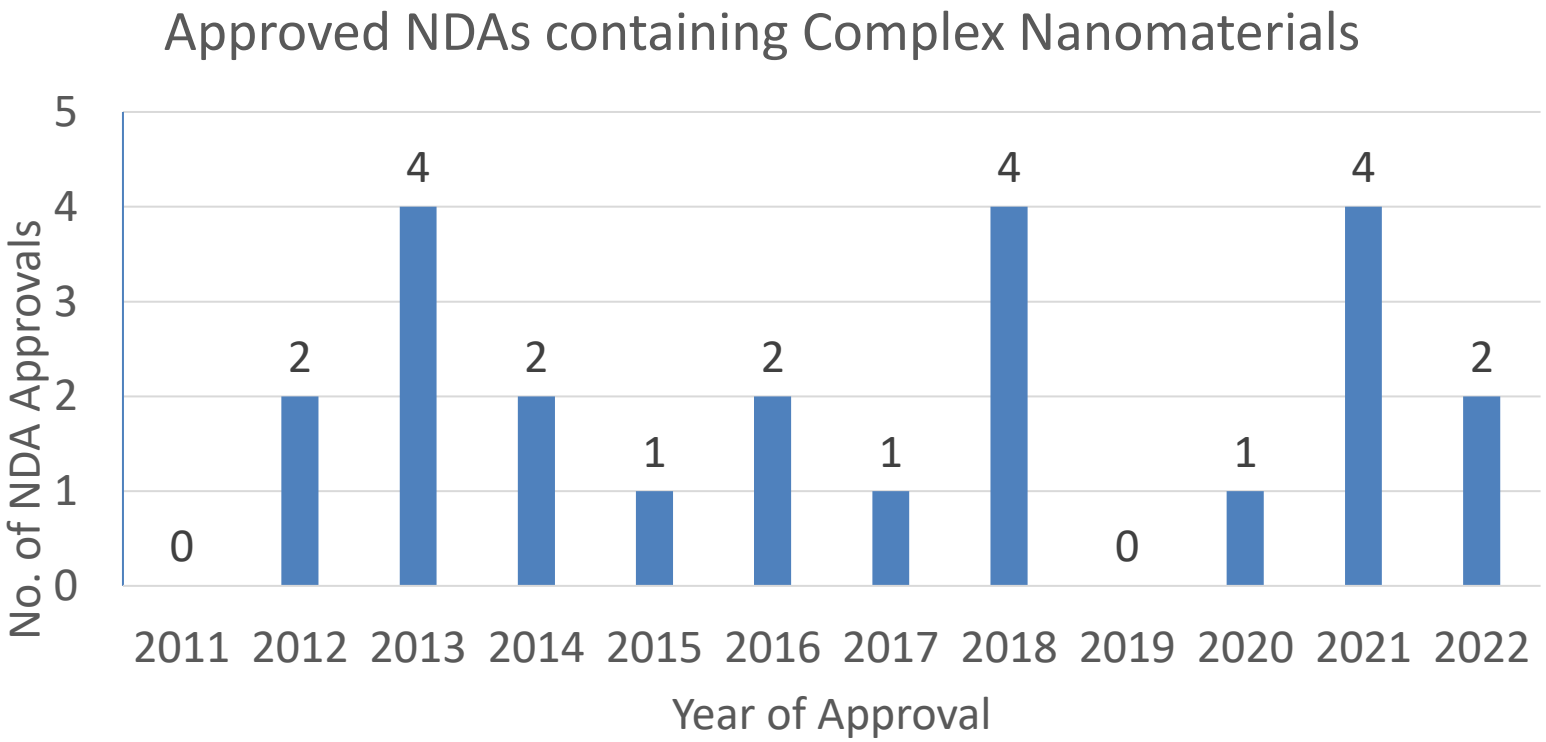






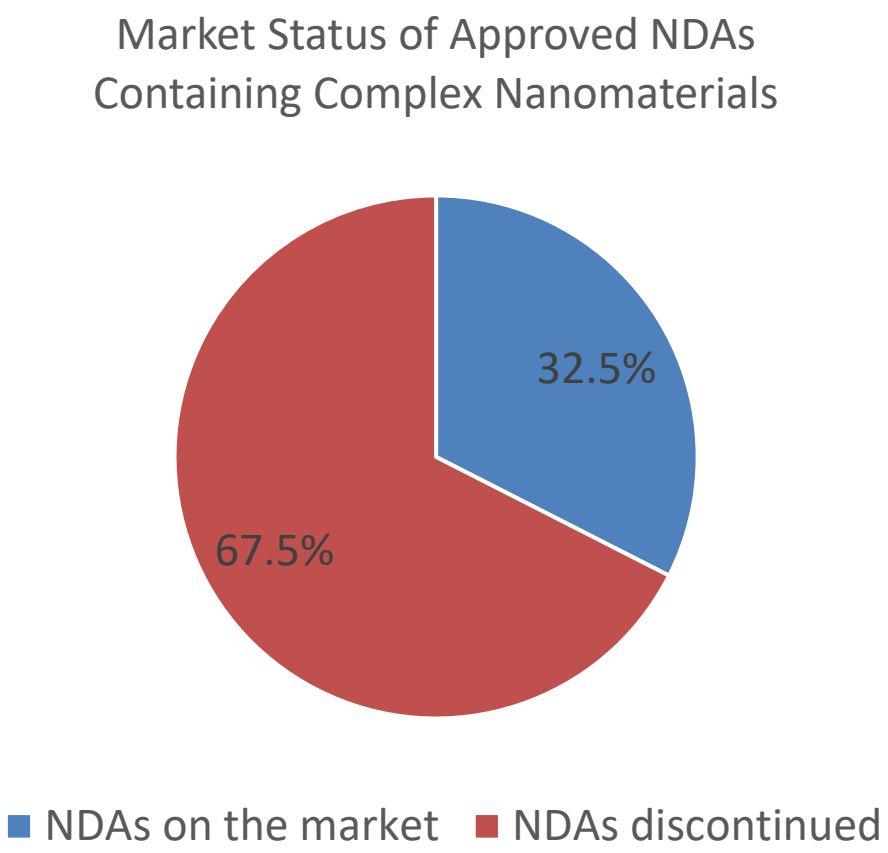


Approved NDAs Containing Complex Nanomaterials between 2011 and 2022



[Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (fda.gov)]

Market Status of Approved NDAs Containing Complex Nanomaterials



Diverse Dosage Forms and Administration Routes of Complex Nanomaterials

Dosage forms
Emulsion
Liposome
Gel
Powder for suspension
Injection
Solution
Lipid complex injection

Administration routes
Intravenous
Ophthalmic
Subcutaneous
Periodontal
Topical
Inhalation

Increased Complexity of Approved NDAs Containing Complex Nanomaterials

- Complex dosage form with two APIs encapsulated
- Complex dosage form, complex drug-device combination product, and complex route of delivery
- Complex API and complex dosage form

Vyxeos® (daunorubicin and cytarabine) 44 mg/100 mg per vial liposome for injection

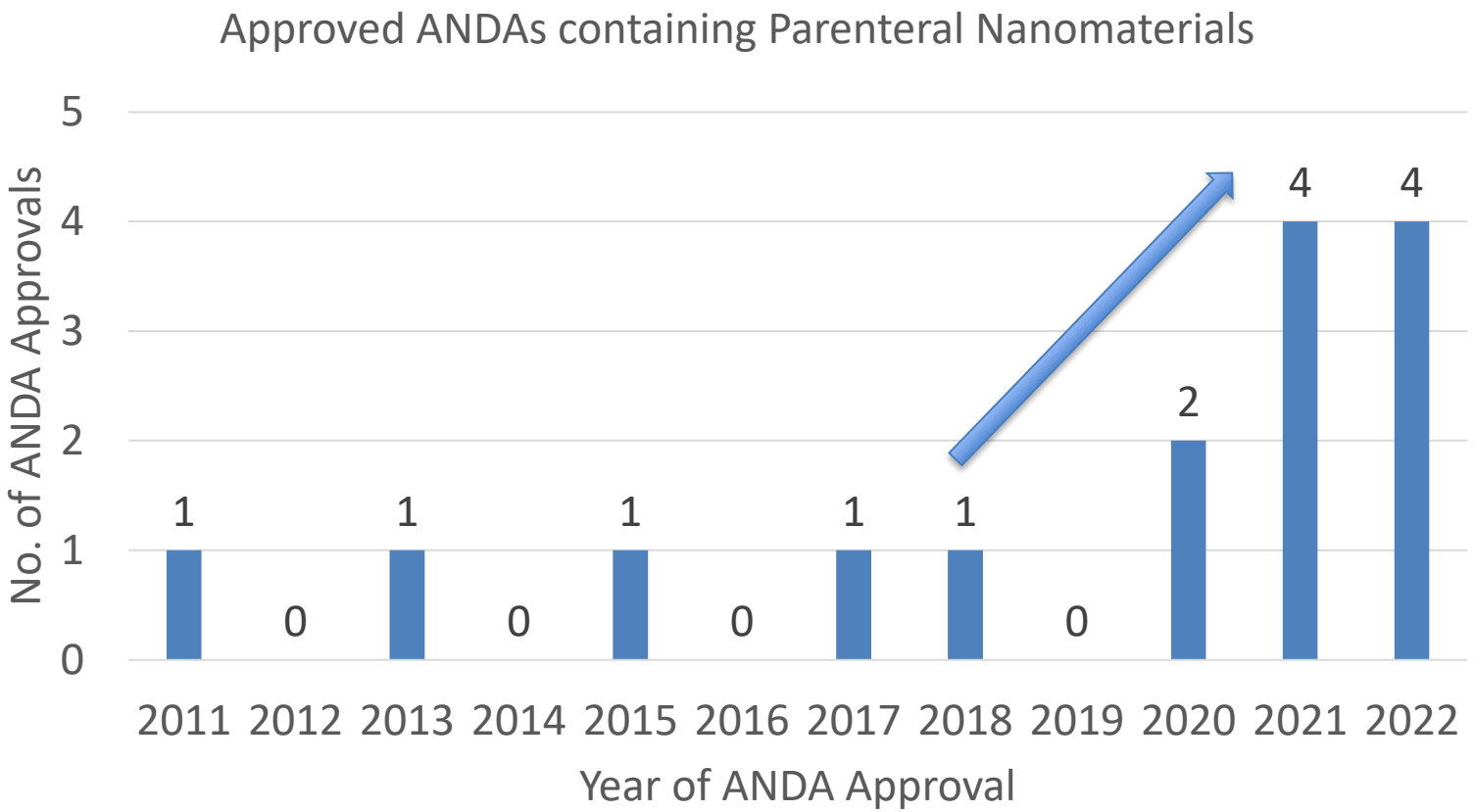
Secondary AML Treatment | VYXEOS® (daunorubicin and cytarabine) (vyxeospro.com)

Dosing | ARIKAYCE® (amikacin liposome inhalation suspension) (arikaycehcp.com)

onpattro™ (patisiran) lipid complex injection

Alnylam Announces First-Ever FDA Approval of an RNAi Therapeutic, ONPATTRO™ (patisiran) for the Treatment of the Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis in Adults | Business Wire

Approved ANDAs Containing Complex Nanomaterials between 2011 and 2022

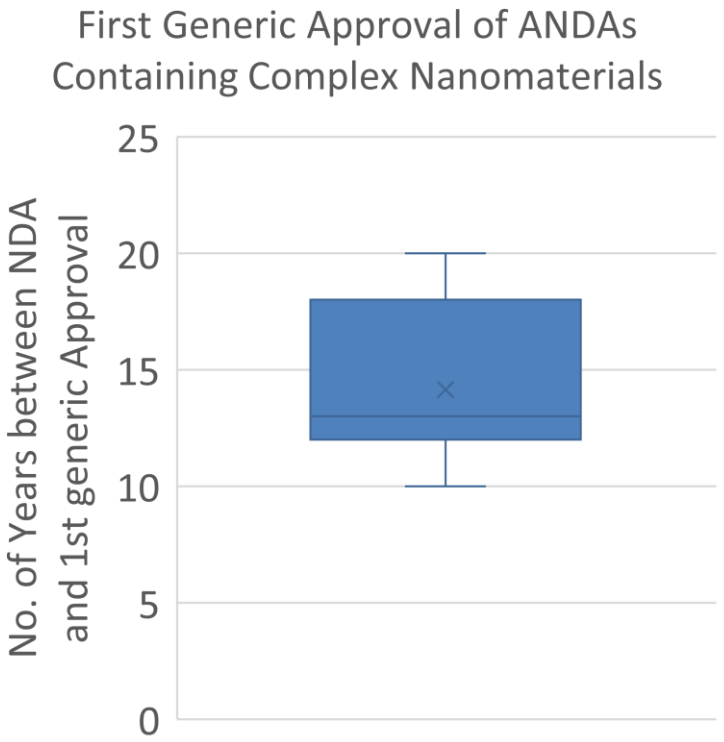


[Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (fda.gov)]

Availability of Generics Containing Complex Nanomaterials

Drug Product	No. of ANDAs Approved by Dec 2022
Doxorubincin HCl Liposome Injection	5
Propofol Emulsion	8
Difluprednate Emulsion	3
Amphotericin B Liposome Injection	2
Ferric Oxyhydroxide (Sodium ferric gluconate injection in sucrose)	1
Ferumoxytol Injection	1
Cyclosporine Emulsion	1

<20% of approved NDAs containing complex nanomaterials have generics available



Guidances Available to Support Development of Complex Generics Containing Nanomaterials

Guidance List

- Agency Guidance

Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology | FDA

- CDER and CBER Guidance

Drug Products, Including Biological Products, that Contain Nanomaterials - Guidance for Industry | FDA

- Class-specific guidance

Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation | FDA

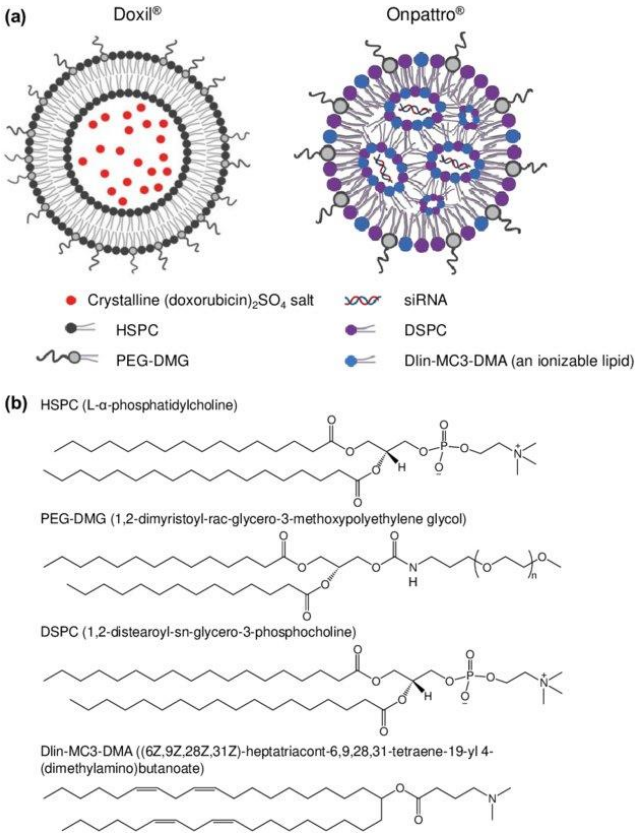
- Product-Specific Guidance (PSG)

Product-Specific Guidances for Generic Drug Development

FDA Upcoming PSGs for Generic Drug Product Development

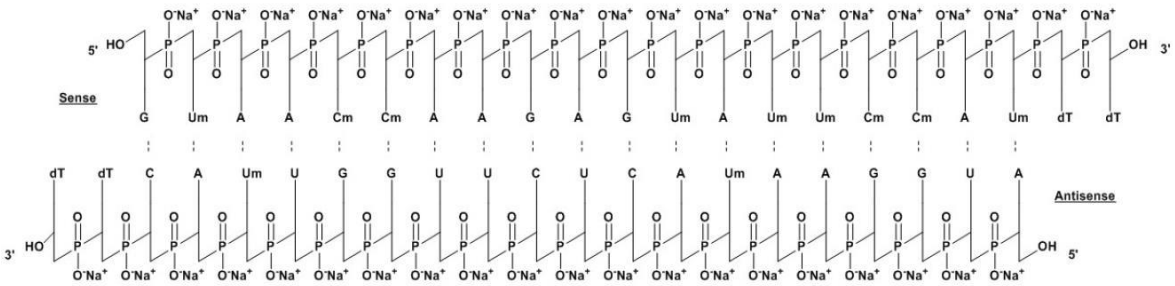
Patisiran Sodium Lipid Complex Injection

Complex Nanomaterials



[Figures cited from Lipid-Based Nanoparticles in the Clinic and Clinical Trials: From Cancer Nanomedicine to COVID-19 Vaccines (researchgate.net)]

Complex API



A, adenosine; C, cytidine; G, guanosine; U, uridine; Cm, 2'-*O*-methylcytidine; Um, 2'-*O*-methyluridine; dT, thymidine

Indication: Polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults

Administration route: intravenous infusion

Lipid complex injection: 10 mg/5 ml white to off-white, opalescent, homogeneous solution in a single-dose vial

Initial U.S. approval: 2018

Draft Guidance on Patisiran Sodium

November 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Patisiran sodium
Dosage Form; Route:	Solution; intravenous
Strength:	EQ 10 mg base/5 mL (EQ 2 mg base/mL)
Recommended Studies:	Comparative characterization studies to support active ingredient sameness, one in vivo bioequivalence study with pharmacokinetic endpoints, one in vitro bioequivalence study with particle size distribution endpoints, and supportive physicochemical characterization studies

This guidance provides recommendations for developing generic patisiran sodium intravenous solution containing patisiran sodium as the Active Pharmaceutical Ingredient (API). It includes recommendations for demonstrating API sameness and bioequivalence.

In addition, generic applicants are advised to contact the FDA for questions related to generic development of patisiran including questions on immunogenicity and inflammation risk assessment, and comparability of impurities in the test product.

Recommendations to support API sameness:

For a comprehensive characterization to support sameness between the test API and the API from the Reference Listed Drug (RLD), FDA recommends that potential applicants develop and use appropriately validated orthogonal analytical methods to perform side-by-side comparative testing of the test API and the API from the RLD product. A minimum of three batches of the test API and three batches of the API from the RLD should be characterized to assess API sameness and robustness in the manufacturing process. The API sameness can be established by evaluating the equivalence in the following:

1. Primary sequence, chemical structure, and composition

The patisiran drug substance duplex is formed by Watson-Crick base pairing of the antisense and the sense single strand intermediates. The primary sequence of the sense and antisense strands in the test patisiran API can be controlled through each elongation cycle in the API synthesis. Sequence, chemical structure and composition of the single strand intermediates should be investigated and confirmed with a broad range of orthogonal analytical methods.

The test API sequence, chemical structure and composition should be compared to that of the API from the RLD using a broad range of orthogonal analytical methods with sufficient sensitivity, discriminating and resolving power, that could include but are not limited to the following:

a. Mass spectrometry (MS), including tandem mass spectrometry (MS/MS)
b. Nuclear magnetic resonance (NMR) spectroscopy
c. Liquid chromatography (LC)
d. Flame atomic absorption spectroscopy (FAAS)
e. Duplex melting temperature (Tm)

2. Physicochemical properties

Comparative physicochemical characterizations of the test and RLD products should be performed using methods that could include but are not limited to the following:

a. Circular dichroism (CD) spectroscopy
b. Differential scanning calorimetry (DSC)
c. Size exclusion chromatography (SEC)
d. Sedimentation velocity analytical ultracentrifugation (SV-AUC)

If the sameness between the test and reference products can be adequately demonstrated using validated alternative analytical methods, applicants may submit comparative data for test and reference products along with appropriate justification as part of their product characterization within their Abbreviated New Drug Application (ANDA). In such case, comprehensive method validation data should be submitted to demonstrate the adequacy of the selected methods in demonstrating the sameness between the test and reference product.

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
   Design: Single dose, randomized, parallel, in vivo
   Strength: Eq 10 mg Base/5 mL (Eq 2 mg Base/mL)
   Dose: 0.3 mg/kg for subjects weighing ≤100 kg, or 30 mg for subjects weighing >100 kg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments:
   a. The product should be administered according to the current RLD label. All subjects should consent to and receive relevant premedication prior to the administration of the test and reference products to reduce the risk of infusion-related reactions (IRRs). Closely monitor subjects during the infusion for signs

and symptoms of IRRs. If any events of IRRs occur, determine the management as clinically appropriate (e.g., stopping the infusion and use of additional medications for symptomatic treatment).

b. Sufficient sampling points should be made to capture the biphasic PK profile.[1]

Analytes to measure: Lipid nanoparticle (LNP)-entrapped patisiran siRNA in plasma

Bioequivalence based on (90% CI): AUC and Cmax for LNP-entrapped patisiran siRNA

One in vitro bioequivalence study with particle size distribution endpoints:

1. Type of study: Particle size distribution
   Design: In vitro testing on at least three batches of both test and reference products

Parameters to measure: Z-average size and polydispersity index (PDI) or D_{50} and SPAN as appropriate

Bioequivalence based on (95% upper confidence bound): Z-average and PDI or D_{50} and SPAN using the population bioequivalence (PBE) statistical approach. Applicants should provide no less than 10 datasets from 3 batches each of the test and Reference Standard (RS) products to be used in the PBE analysis. For additional information on PBE statistical analysis, refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929).[a]

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testin on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the ANDA.

Additional information:

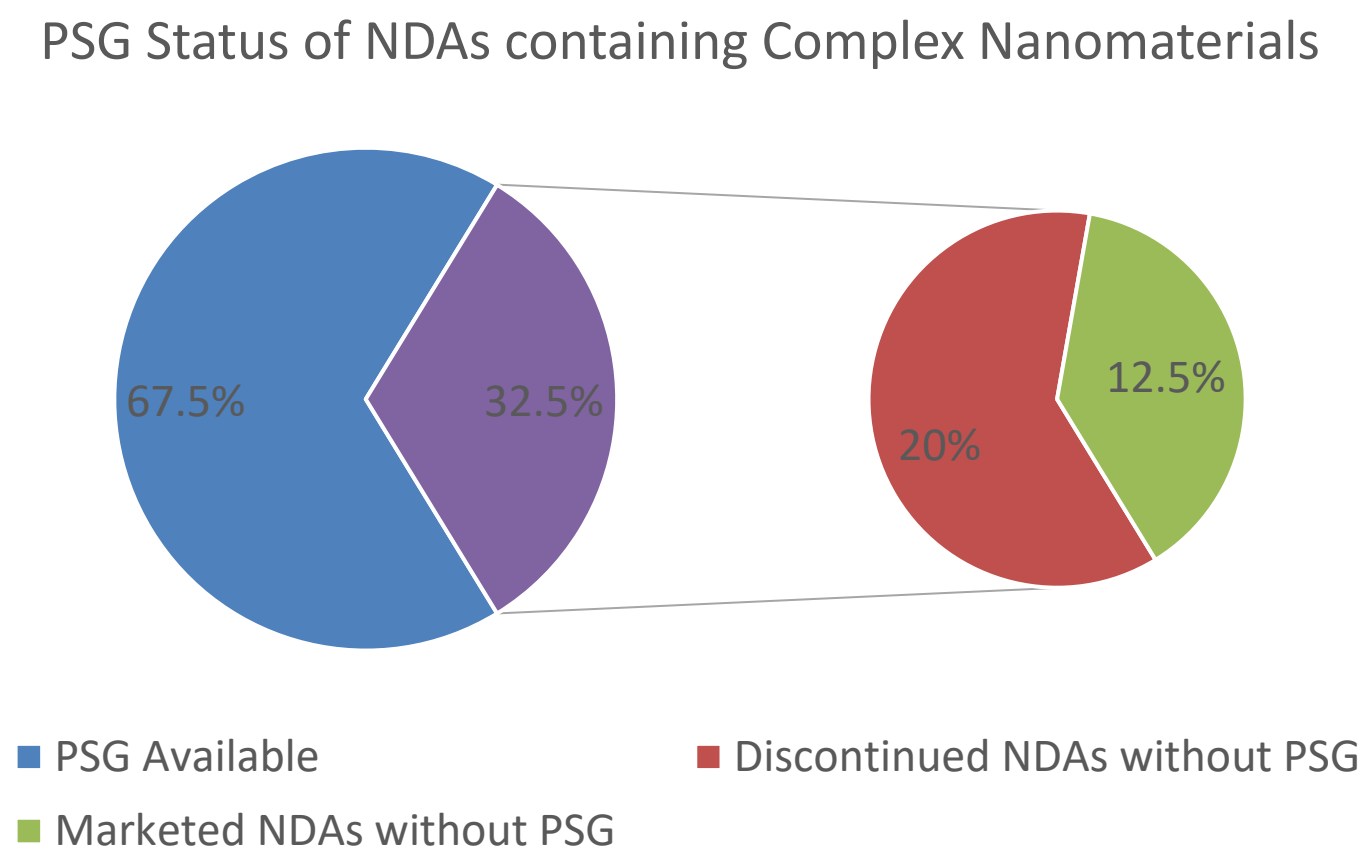
1. The proposed parenteral drug product should be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the RLD. An applicant may seek approval of a drug product that differ from the RLD in preservative, buffer or antioxidant if the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[4]

2. Lipid excipients are critical in the lipid nanoparticle drug products. Although not a liposomal drug product, for additional information on the chemistry, manufacturing and control of the lipid components, refer to the most recent version of the FDA guidance for industry on *Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation.*[b]

3. Comparative physicochemical characterization of test product and RS product with appropriately validated analytical methods. These in vitro characterization studies should be conducted on at least three batches of the test[5] and RS products. At least one test batch should be produced by the commercial scale process and used in the in vitro and in vivo bioequivalence studies. The attributes to be characterized should include, but are not limited to, the following:
   a. LNP drug product composition: lipid content, drug-to-lipid ratio, and siRNA location (e.g., free, surface-bound, and entrapped siRNA, if applicable)
   b. Physicochemical properties of the drug product: pH, osmolality, density, viscosity, PEG layer thickness, electrical surface charge, and LNP morphology
   c. In-vitro release of siRNA from patisiran drug product
   d. In-vitro bioassay for transthyretin (TTR) mRNA knockdown with IC50 value being determined

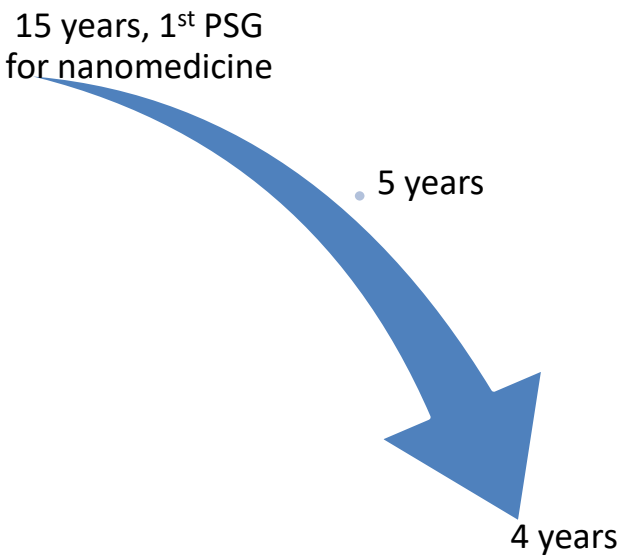
[1] X. Zhang et al., Pharmacokinetics of patisiran, the first approved RNA interference therapy in patients with hereditary transtryretin-mediated amyloidosis. The Journal of Clinical Pharmacology 2020, 60(5) 573-585
[2] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product.
[4] 21CFR 314.94(a)(9)(iii)

PSG Status of NDAs containing Complex Nanomaterials



Timely Development of PSGs for Products Containing Complex Nanomaterials

Product name	Year of NDA approval	Year of 1st PSG publication
Doxorubicin HCl liposome injection	1995	2010
Cytarabine and Daunorubicin liposome injection	2017	2022
Patisiran sodium lipid complex injection	2018	2022



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Regulatory Research for Products Containing Complex Nanomaterials

Example GDUFA Regulatory Research Projects

Extramural

• Grant (1U01FD007363)

Development of Advanced Analytical Methods for the Characterization of Iron Carbohydrate Complex-Ferric Derisomaltose with Sarah L. Michel at University of Maryland Baltimore.

• Contract (75F40121C00189)

Characterization of Carboxymaltose Variability and Interactions in Ferric Carboxymaltose Complexes with Eric J. Munson at Purdue University.

• Grant (5U01FD005946-04)

Hyperspectral Interferometric Scattering Microscopy for Characterizing Nanoparticle-Based Therapeutics with William E. Bentley, James E. Polli at University of Maryland (Baltimore).

• Contract (75F40119C10139)

MIDD Approach to Identify Critical Quality Attributes and Specifications for Generic Nanotechnology Products with Jessie L.S. Au at Institute of Quantitative Systems Pharmacology (IQSP).

• Contract (75F40119S30028)

Nanofluidic Slit Devices for Measuring Nano-Particle Drug Concentration to Improve Complex Drug Regulation With Samuel Stavis at the NIST Center for Nanoscale Science and Technology.

Intramural

Assessing New Analytical Methods for Characterizing Characterization of Complex Nanotechnology Drug Products

Product-Specific Guidance (PSG) for Iron Sucrose (N021135) (2013 Version)

Active Ingredient: Iron Sucrose
Dosage Form; Route: Injectable; intravenous
Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, randomized parallel in vivo study
Strength: EQ 100 mg Iron/5 mL (Dose 100 mg)
Subjects: Healthy males and females, general populations
Additional comments: The products should be administered undiluted as a slow intravenous injection dose of 100 mg over 5 minutes.

Analytes to measure: Measure each of the following:

1) Total iron in serum

2) Transferrin-bound iron in serum

Bioequivalence based on (90% CI):

Maximum value of the difference in concentration between Total iron and Transferrin-bound iron over all time points measured; and

difference in AUC between Total iron and Transferrin-bound iron

2. Type of study: Particle size distribution
Design: In vitro testing on at least three lots of both test and reference products

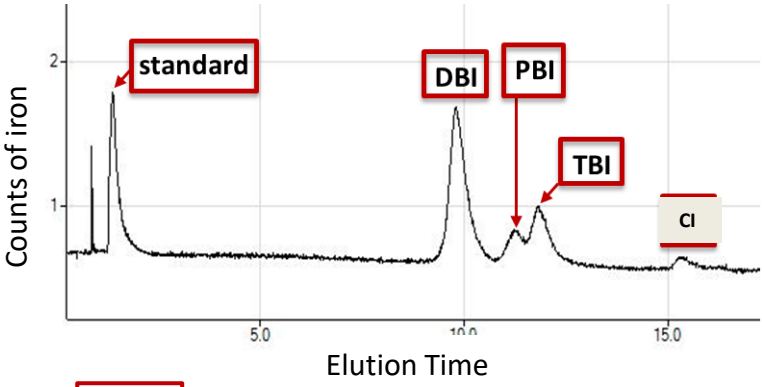
Parameters to measure: D10, D50, D90

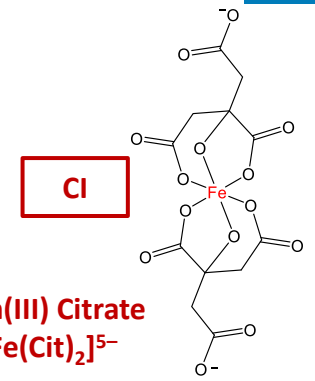
Bioequivalence based on: D50 and SPAN [i.e. (D90-D10)/D50] or polydispersity index using the population bioequivalence statistical approach.

- Direct measurements of different iron species in vivo
- Feasibility of crossover study design
- Non-transferrin bound iron (NTBI) in vivo
  - NTBI may induce toxicity if taken up by liver, heart, …

Iron Speciation

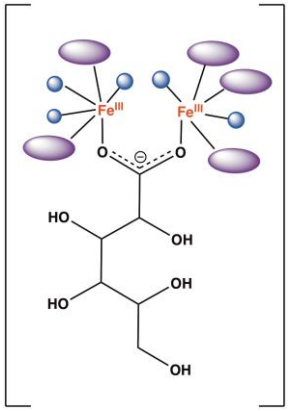
- An LC-ICP-MS method was developed for the first time to directly measure the drug-bound iron.
- No significant differences were observed between generic and brand sodium ferric gluconate in TI, TBI, DBI, and NTBI levels.
- 14-28 day seems to be a reasonable washout period in a crossover bioequivalence (BE) study for iron complex products based on observed ferritin and TIBC levels.



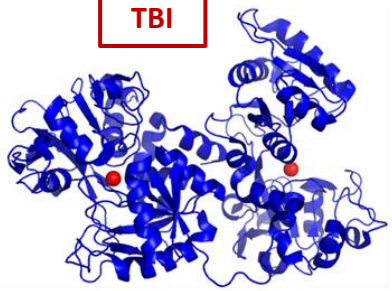


Iron(III) Citrate
$[Fe(Cit)_2]^{5-}$

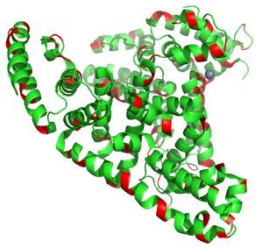
DBI



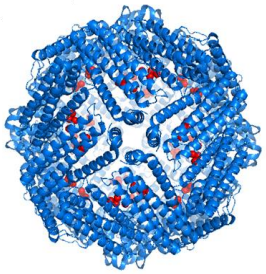
TBI



PBI = ABI + FBI



Albumin



Ferritin

Evaluation of Iron Species in Healthy Subjects Treated with Generic and Reference Sodium Ferric Gluconate (U01FD005266)
Drs. Sarah Michel and James Polli, University of Maryland

Snapshots of Iron Speciation: Tracking the Fate of Iron Nanoparticle Drugs via a Liquid Chromatography-Inductively Coupled Plasma-Mass Spectrometric Approach - PubMed (nih.gov)

DBI: Drug bound iron
PBI: Protein bound iron
TBI: Transferrin bound iron
CI: Iron citrate
ABI: Albumin bound iron
FBI: Ferritin bound iron

PSG for Ferric Oxyhydroxide Injection (N021135)(2021 Version)

Active Ingredient: Ferric oxyhydroxide

Dosage Form; Route: Injectable; intravenous

Recommended Studies: Two studies

1.Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
Design: Single-dose, randomized in vivo study
Strength: EQ 100 mg Iron/5 mL (Dose 100 mg)
Subjects: Healthy males and females
Additional comments: The products should be administered undiluted as a slow intravenous injection dose of 100 mg over 5 minutes for both the test and reference products at the same rate. The in vivo BE study may be parallel or crossover design. A replicate crossover study may be an appropriate alternative to the parallel or nonreplicated crossover study. BE can be demonstrated using method in either option 1 or option 2.

Analytes to measure (option 1): Iron in the form of colloidal ferric oxyhydroxide in serum when a direct measurement of the colloidal form is achievable.

Bioequivalence based on (90% CI): iron in ferric oxyhydroxide colloid in serum

Analytes to measure (option 2): When direct measurement of iron in the form of colloidal ferric oxyhydroxide is not possible, measure each of the following:

1) Total iron in serum
2) Transferrin-bound iron in serum

Bioequivalence based on (90% CI):

- Maximum value of the difference in concentration between Total iron and Transferrin-bound iron over all time points measured; and
- Difference in AUC between Total iron and Transferrin-bound iron

Product-Specific Guidances for Generic Drug Development (fda.gov)

Direct Quantification of Unencapsulated Doxorubicin (Dox) Using Capillary Electrophoresis

OGD - Office of Regulatory Affairs (ORA) Collaboration

Separation of unencapsulated and nanomaterials associated drug may induce drug leakage

Separation process is lengthy

Simultaneous separation and quantification of unencapsulated and liposome encapsulated drugs

International Journal of Pharmaceutics 549 (2018) 109–114

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Direct quantification of unencapsulated doxorubicin in liposomal doxorubicin formulations using capillary electrophoresis

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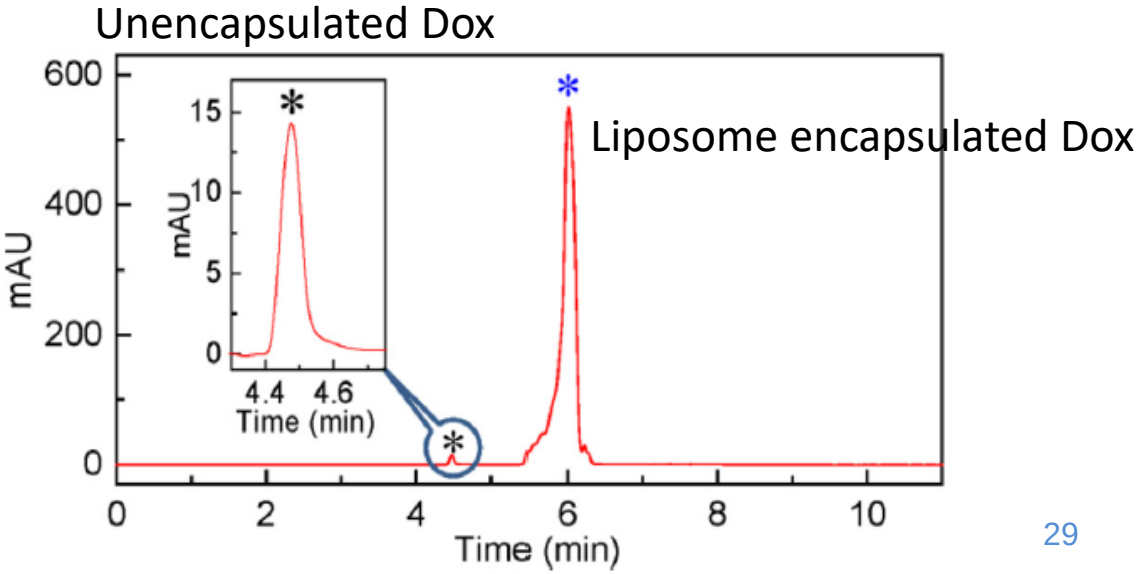
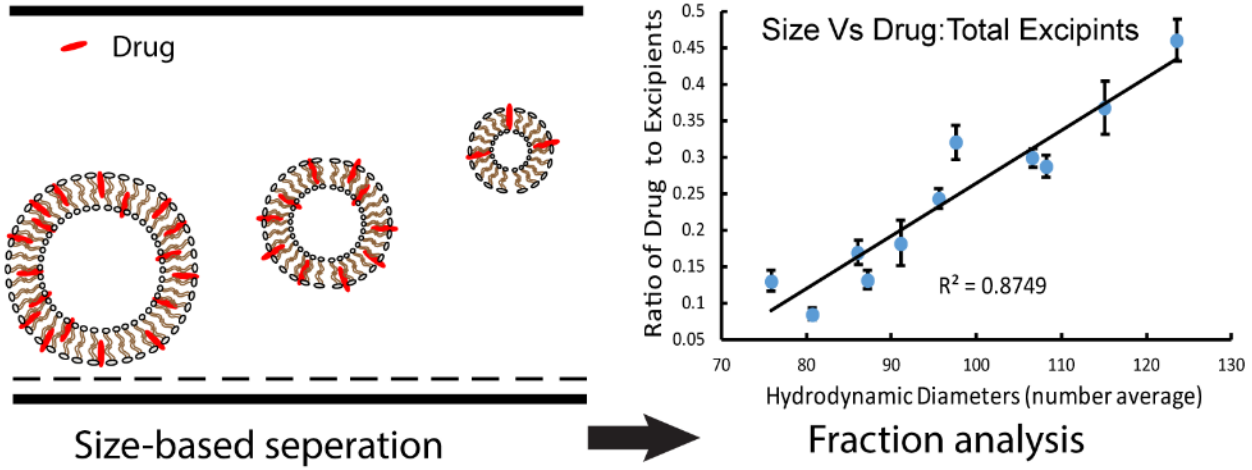


Quantification of Lipid Excipients and Active Pharmaceutical Ingredients (APIs) in Liposomes



International Journal of Pharmaceutics 569 (2019) 118603

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Evaluation of size-based distribution of drug and excipient in amphotericin B liposomal formulation

Desiree Van Haute[a], Wenlei Jiang[b,*], Thilak Mudalige[a,*]

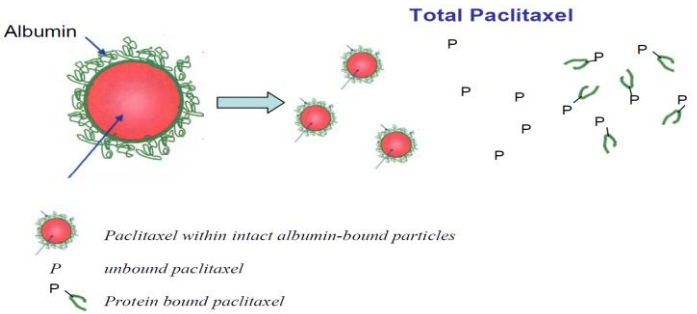
[a] Arkansas Laboratory, Office of Regulatory Science, Office of Regulatory Affairs, US Food and Drug Administration, Jefferson, AR 72079, United States
[b] Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 20993, United States

Global Regulatory Efforts to Facilitate Development of Complex Generics Containing Nanomaterials

Differed Approval Standards for Complex Generics Containing Nanomaterials

Proprietary Name
ABRAXANE®
Non-Proprietary Name
Paclitaxel protein-bound particles for injectable suspension
Ingredients
Paclitaxel, human serum albumin (HSA)

Indications	Dosage
Metastatic Breast Cancer	260 mg/m^2
Non-Small Cell Lung Cancer	100 mg/m^2
Adenocarcinoma of the Pancreas	125 mg/m^2



Generics available in EU but not in US
There was a 505 b2 approval in US.

U.S. FDA Recommendation

1. The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the corresponding reference listed drug product (RLD).

2. Test should have the same in vitro characteristics as the reference product prior to conducting any bioequivalence study for submission.

3. In vivo bioequivalence study with pharmacokinetic (PK) endpoints

Design: Single-dose, two-way crossover, in vivo in breast cancer patients

Analytes to measure: Unbound and total paclitaxel in plasma

Bioequivalence based on (90% CI): AUC and Cmax for unbound and total paclitaxel

4. In vitro particle size distribution

Parameters to measure: D10, D50, and D90

Bioequivalence based on (95% upper confidence bound): Population bioequivalence based on D50 and SPAN [(D90-D10)/D50]

EMA Review Experiences

1. "the concentration of Paclitaxel is the same and the concentration of the excipient albumin is similar."

2. "To further demonstrate comparability between the proposed product and the reference product Abraxane, the following physicochemical characteristics were compared (see quality assessment)"

3. "Waiver for bioequivalence studies/clinical studies on the basis of the qualitative and quantitative comparability with the reference product and based on its rapid dissociation after dilution."

4. Comparative non-clinical studies of the pharmacokinetics and of the anti-tumor effects

https://www.ema.europa.eu/en/documents/assessment-report/pazenir-epar-public-assessment-report_en.pdf

Global Dialogues Help Communicate Scientific Advancements and Bridge Gaps for Complex Generic Approval

- Generic Drug Cluster (Launched in June 2021)
- FDA-EMA Parallel Scientific Advice Pilot Program for Complex Generic/Hybrid Products (Launched in September 2021)
  Global Generic Drug Affairs | FDA
- Global Bioequivalence Harmonization Initiative Workshop
  https://gbhi.eufeps.org/
- ICH Generic Drug Discussion Group
  - https://database.ich.org/sites/default/files/ICH_GDG_Remit_Final_2019_0130.pdf
  - https://database.ich.org/sites/default/files/DG_GDG_WorkPlan_2021_0210.pdf
- International Pharmaceutical Regulators Programme (IPRP) Nanomedicine Working Group
  http://www.iprp.global/working-group/nanomedicines

GBHI Conference

Goal: Facilitate scientific discussion on the topics that can foster harmonization of the bioequivalence (BE) requirements

Apr 2018 GBHI topics

- Necessity of multiple dose studies in BE testing
- BE of transdermal delivery system
- Liposome parenteral preparations

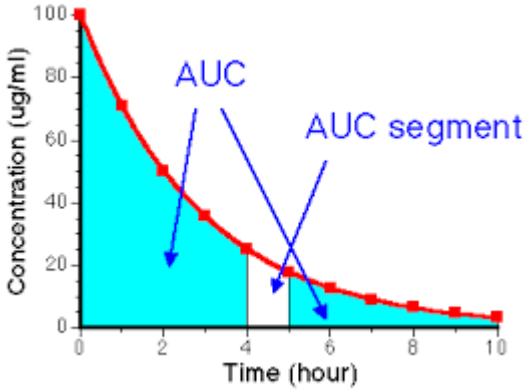
Continued Efforts to Promote Harmonization on Nanomedicine Evaluation Criteria

U.S. FDA Doxorubicin HCl liposomes Product-Specific Guidance (Recommended 2010, most recent revision 2022)

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

Reached agreements on analytes to be measured

Still debate on pAUC necessary or not?



European Medicines Agency (EMA) Doxorubicin HCl liposomes Product-Specific Guideline (Recommended 2018)

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/06/WC500251058.pdf

International Pharmaceutical Regulators Programme (IPRP) Nanomedicine Working Group

Members:

- ANMAT, Argentina
- ANVISA, Brazil
- COFEPRIS, Mexico
- EC/EMA, Europe
- EDA, Egypt
- U.S. FDA, United States
- Health Canada, Canada
- HSA, Singapore
- MFDS, Republic of Korea
- PMDA, Japan
- SFDA, Saudi Arabia
- Swissmedic, Switzerland
- TFDA, Taiwan
- TGA, Australia
- TITCK, Turkey

- Non-confidential information sharing, regulatory harmonization or convergence
- Regulatory cooperation
- Collaboration of training organization between international regulators
- Promotion of potential consensus on standards

IPRP NWG Activities

- Liposome survey

  Conduct a survey to analyze the regulatory landscape for liposomal products, identify the needs of both research and standards development, and enhance the potential for harmonisation of regulatory requirements.

- Zoom Nano Webinars

  2022 Theme: Scientific and Regulatory Considerations for Generic and Follow-on Nanomedicines

  -2023 Theme: Regulation of Lipid Nanoparticle (LNP) Products

- Hot topics

  Excipients containing nanomaterials

  Determination of excipients in products containing nanomaterials

  Impact of lipid degradation products on vaccine efficacy

Summary

- Progress has been made in the regulatory research, guidance development, and application approval of complex generic drug products containing nanomaterials.
- Streamlined process was established to identify research needs, translate research results to guidance development, and facilitate approval of complex generic products containing nanomaterials.
- Global regulatory collaborations help accelerate such progress and harmonization of scientific recommendations for complex generic drug products containing nanomaterials.

Acknowledgements

- Office of Research and Standards
- Office of Generic Drugs
- Office of Pharmaceutical Quality
- Office of Regulatory Affairs
- University of Maryland