

# Complex Generics Containing Nanomaterials: Developments in 2021 and 2022

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# Complex Products



According to the **GDUFA II 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>

*Complex active pharmaceutical ingredient (API)*

- 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](#)

## 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)



# Developments Overview

Complex drug products containing nanomaterials

- Approval of Abbreviated New Drug Applications (ANDAs) and New Drug Applications (NDAs)
- Guidance development
- GDUFA research
- Global regulatory efforts

# 2020-Present Approvals of ANDAs Containing Nanomaterials



Application Number	Applicant Full Name	Active Ingredient	Dosage Form	Route	Strength	Approval Date	RLD Approval
205894	MYLAN PHARMACEUTICALS INC	CYCLOSPORINE	EMULSION	OPHTHALMIC	0.05%	2022-02-02	2002-12-23
212514	SUN PHARMA INDUSTRIES LTD	AMPHOTERICIN B	INJECTABLE, LIPOSOMAL	INJECTION	50MG/VIAL	2021-12-14	1997-08-11
211526	AMNEAL EU LTD	DIFLUPREDNATE	EMULSION	OPHTHALMIC	0.05%	2021-11-17	2008-06-23
207228	AYANA PHARMA LTD	DOXORUBICIN HYDROCHLORIDE	INJECTABLE, LIPOSOMAL	INJECTION	20MG/10ML (2MG/ML)	2021-10-12	1995-11-17
207228	AYANA PHARMA LTD	DOXORUBICIN HYDROCHLORIDE	INJECTABLE, LIPOSOMAL	INJECTION	50MG/25ML (2MG/ML)	2021-10-12	1995-11-17
211776	CIPLA LTD	DIFLUPREDNATE	EMULSION	OPHTHALMIC	0.05%	2021-08-09	2008-06-23
206604	SANDOZ INC	FERUMOXYTOL	SOLUTION	INTRAVENOUS	EQ 510MG IRON/17ML (EQ 30MG IRON/ML)	2021-01-15	2009-06-30
212299	ZYDUS WORLDWIDE DMCC	DOXORUBICIN HYDROCHLORIDE	INJECTABLE, LIPOSOMAL	INJECTION	50MG/25ML (2MG/ML)	2020-09-10	1995-11-17
212299	ZYDUS WORLDWIDE DMCC	DOXORUBICIN HYDROCHLORIDE	INJECTABLE, LIPOSOMAL	INJECTION	20MG/10ML (2MG/ML)	2020-09-10	1995-11-17

[Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations \(fda.gov\)](https://www.fda.gov/orange-book)

# 2020-Present Approvals of NDAs Containing Nanomaterials

Application	Applicant Full Name	Trade Name	Active Ingredient	Dosage Form	Route	Strength	Approval Date
NDA215395	INVAGEN PHARMACEUTICALS INC	LANREOTIDE ACETATE	LANREOTIDE ACETATE	SOLUTION	SUBCUTANEOUS	EQ 120MG BASE/0.5ML (EQ 120MG BASE/0.5ML)	2021-12-17
NDA215395	INVAGEN PHARMACEUTICALS INC	LANREOTIDE ACETATE	LANREOTIDE ACETATE	SOLUTION	SUBCUTANEOUS	EQ 60MG BASE/0.2ML (EQ 60MG BASE/0.2ML)	2021-12-17
NDA215395	INVAGEN PHARMACEUTICALS INC	LANREOTIDE ACETATE	LANREOTIDE ACETATE	SOLUTION	SUBCUTANEOUS	EQ 90MG BASE/0.3ML (EQ 90MG BASE/0.3ML)	2021-12-17
NDA213312	AADI BIOSCIENCE INC	FYARRO	SIROLIMUS	POWDER	INTRAVENOUS	100MG/VIAL	2021-11-22
NDA214965	SANTEN INC	VERKAZIA	CYCLOSPORINE	EMULSION	OPHTHALMIC	0.1%	2021-06-23
NDA210583	BAUDAX BIO INC	ANJESO	MELOXICAM	SOLUTION	INTRAVENOUS	30MG/ML (30MG/ML)	2020-02-20
NDA203565	AMERICAN REGENT INC	INJECTAFER	FERRIC CARBOXYMALTOSE	SOLUTION	INTRAVENOUS	1GM IRON/20ML (50MG IRON/ML)	2021-04-28
NDA 203565	AMERICAN REGENT INC	INJECTAFER	FERRIC CARBOXYMALTOSE	SOLUTION	INTRAVENOUS	500 MG IRON/10ML (50MG IRON/ML)	2020-10-28

# 2020-Present Product-specific Guidances (PSGs) for Nanomedicine Products



## **New Draft Guidance**

Irinotecan HCl injection, liposomal (Feb 2022)

Meloxicam Injection (May 2021)

Degarelix Acetate Powder Subcutaneous (March 2021)

Aprepitant Intravenous Emulsion (June 2020)

Fish Oil Triglycerides Intravenous Emulsion (June 2020)

Clevidipine Intravenous Emulsion (March 2020)

Amino Acids; Calcium Chloride; Dextrose; Magnesium Sulfate; Potassium Chloride;  
Sodium Acetate; Sodium Glycerophosphate; Soybean Oil Intravenous Emulsion (March  
2020)

## **Revised Draft Guidance**

Ferric Oxyhydroxide Injection (September 2021)

Amphotericin B Injection, Liposomal (August 2020)

[Product-Specific Guidances for Generic Drug Development | FDA](#)

# GDUFA Research FY2021 and FY2020



## **New Grant(s) and Contract(s)**

- 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.

## **Continuing Grant(s) and Contract(s)**

- 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.

## **Completed Grant(s) and Contract(s)**

- Contract (75F40120C00055)

*Evaluation of Critical Process Parameters for the Preparation of Amphotericin B that Influence Toxicity* with Nelson Landrau at Landrau Scientific Innovations, LLC.

# 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

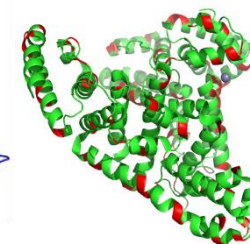
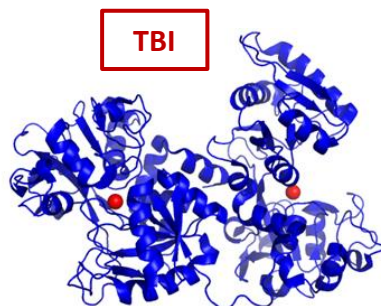
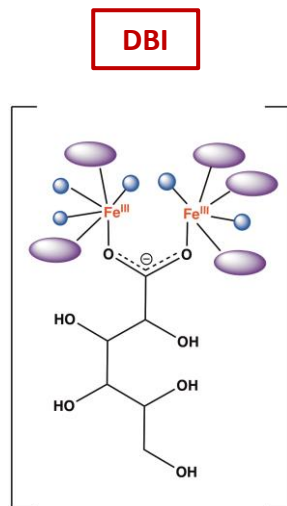
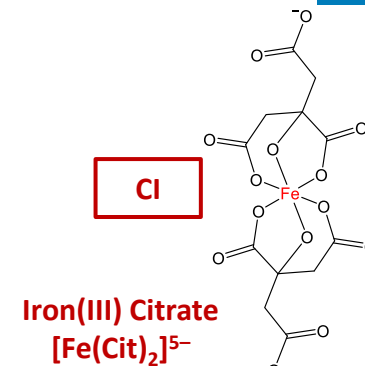
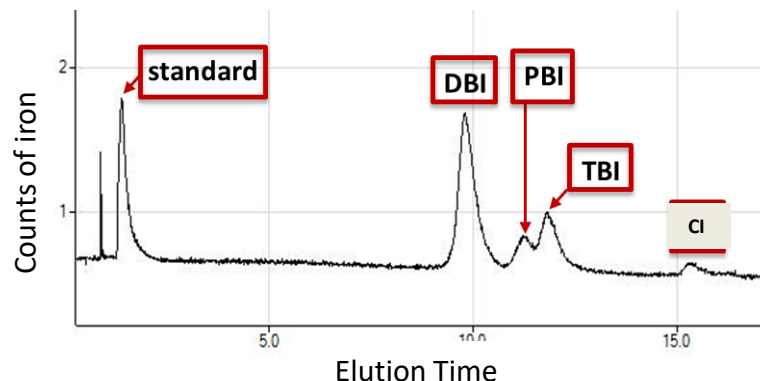
**Parameters to measure:** D10, D50, D90

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

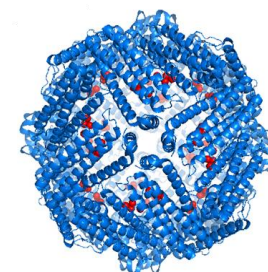
- Direct measurements of different iron species in vivo
- Feasibility of crossover study design
- Non-transferrin bound iron (NTBI) in vivo
  - NTBI may induce toxicity if taken up by liver, heart, ...

# 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.



**PBI = ABI + FBI**



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 \(fda.gov\)](https://www.fda.gov/oc/ohrt/guidances-for-generic-drug-development)

# Global Regulatory Efforts

**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](#)

**International Pharmaceutical Regulators Programme (IPRP)  
Nanomedicine Working Group**

<http://www.iprp.global/working-group/nanomedicines>

**Global Bioequivalence Harmonization Initiative**

<https://gbhi.eufeps.org/>

# Summary



- Significant progress was 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 regulatory recommendations for complex generic drug products containing nanomaterials.

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