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The evolving landscape of drug products containing nanomaterials in the United States

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Supplementary Table 1. Structure of information gathered for each of the identified drug products containing nanomaterials

Database Fields	Database Field Descriptions
Application Type/Number	Investigational, new or generic drug submissions, e.g. NDA XXXXXX
Referenced Applications	Applications that are referenced by a particular application under consideration
Drug Product Name	Proprietary name, trade name, generic name, e.g. Doxil [®]
Product Description	Formulation information e.g. aqueous suspension of liposomes containing PEGylated doxorubicin HCl
Type of Nanomaterial	Specific platform or structure, e.g. liposome, nanotube, micelle, etc. <i>Note these are internal terms used for the purpose of constructing the</i>

	<i>technical profile and are not reflective of official FDA terminology.</i>
Active Ingredient	Active component in the drug product, e.g. doxorubicin, siRNA, etc.
Excipients	Stabilizers, buffers, lipids, e.g. polysorbate 20, mannitol, etc.
Nanomaterial Constituent	Nanoscale component of the product e.g. API, excipient, carrier, etc.
Nanomaterial <i>In Vivo</i> Function/Property	Product attributes resulting from decreasing the size of the nanomaterial, e.g. increased solubility of the drug substance, prolonged circulation, etc.
Lifecycle	Current application status e.g. NDA-Approved
References Approved Product (Yes/No)	Whether or not the application (505(b)(2) NDA or a 505(j) ANDA) makes a reference to an approved innovator drug product
Referenced Drug Products	Applicable to those submissions (505(b)(2) NDA or a 505(j) ANDA) making a reference to approved innovator drug products
Indication Category	Disease condition intended to be diagnosed, prevented, or treated, e.g. cancer, anemia, etc.
Dosage Form	Physical form in which product will be

	administered, e.g. suspension, tablet, emulsion, etc.
Route of Administration	Path by which a product is delivered into the body, e.g. intravenous, oral, etc.
Particle Size/Range	As reported in the submission for nanomaterials, e.g. mean hydrodynamic diameter ~ 40 nm
Method of Assessment of Particle Size	Technique for determining the size of the nanomaterial, e.g. dynamic light scattering
Other Nanomaterial Attributes/Measures/Characterization	Auxiliary physicochemical analysis, e.g. electron microscopy for size and morphology
Methods of Size Reduction	Size reduction techniques e.g. high pressure homogenization
Sponsor	Name of the company (investigator) that submitted the application
FDA Received Date	Date of submission receipt by CDER
Approval Date	Date of full approval of the submission by the office
Responsible Organization	CDER office or division overseeing development, approval, and regulation of the product, e.g. CDER/OGD

Supplementary Table 2. List of nano-related search terms used as the basis for keyword searches within the CDER registry

Nanocrystal, Nanocrystalline

Nanoemulsion, Emulsion, Microemulsion

Liposomes, Nanoliposomal, Liposomal

Nanoparticles, Nanoparticulate

Dendrimer

Micelles, Micellar

Nanotubes

Nanobubbles

Colloid, Colloidal

Metal

Superparamagnetic iron oxide

Silver colloid

Gold colloid

Gold nanoparticles

Submicron

Iron colloid, Iron particles

Nanosuspension, Suspension

Dispersion, Colloidal dispersion

Nanotechnology, Nano

Aerosol

Complex, Conjugate, Covalent, Non-covalent

PEGylated

Carrier

Entrapped, Encapsulated

Targeting ligand

Lipid particle

Silica particles

Nanoplatelet

Titanium dioxide

Polysorbate 80

Nanodroplets

Lipid nanoparticle

Globule

Supplementary Table 3. CDER approved products (NDAs) containing nanomaterials*

Product Name	Indication	Platform/Type	Approval Year
INFeD [®] (iron dextran injection USP)	Iron deficiency anemia; Iron replacement for blood loss	Iron-Polymer Complex	1974
Intralipid [®] 10% (a 10% I.V. fat emulsion)	Parenteral nutrition	Emulsion	1975
Gris-PEG [®] (griseofulvin ultramicrosize tablets USP)	Fungal infections	Nanocrystal	1975
Kit for the Preparation of Technetium Tc99m Sulfur Colloid Injection	Imaging	Metal-Nonmetal Complex	1978
Intralipid [®] 20% (a 20% I.V. fat emulsion)	Parenteral nutrition	Emulsion	1981
Proferdex [™] (iron dextran injection, USP)	Iron deficiency anemia; Iron replacement for blood loss	Iron-Polymer Complex	1981

Intralipid [®] 30% (a 30% I.V. fat emulsion) (Pharmacy Bulk Package)	Parenteral nutrition	Emulsion	1993
Doxil [®] (doxorubicin hydrochloride liposome injection)	Ovarian cancer; AIDS-related Kaposi's Sarcoma; Multiple Myeloma	Liposome	1995
Neoral [®] (cyclosporine soft gelatin capsules, USP modified)	Prophylaxis of organ rejection in kidney, liver, and heart transplantation	Emulsion	1995
Neoral [®] (cyclosporine oral solution, USP modified)	Prophylaxis of organ rejection in kidney, liver, and heart transplantation	Emulsion	1995
Feridex I.V. [®] (<u>ferumoxides</u> injectable solution)	Imaging	Iron-Polymer Complex	1996
Intralipid [®] 20% (a 20% I.V. fat emulsion) (Pharmacy Bulk Package)	Parenteral nutrition	Emulsion	1996

Bulk Package)			
Taxotere [®] (docetaxel injection concentrate)	Breast cancer; NSCLC; Hormone refractory prostate cancer; Gastric adenocarcinoma; Squamous cell carcinoma of the head and neck cancer	Micelle	1996
GastroMARK [®] (ferumoxsil oral suspension)	Imaging	Iron-Polymer Complex	1996
Amphotec [®] (amphotericin B cholesteryl sulfate complex for injection)	Fungal infections	Liposome	1996
DaunoXome [®] (daunorubicin citrate liposome injection)	Advanced HIV-associated Kaposi's sarcoma	Liposome	1996
Dexferrum [®] (iron dextran injection, USP)	Iron deficiency anemia; Iron replacement for blood loss	Iron-Polymer Complex	1996
Neoral [®] (cyclosporine oral solution, USP)	Rheumatoid arthritis	Emulsion	1997

modified)			
Neoral [®] (cyclosporine soft gelatin capsules, USP modified)	Rheumatoid arthritis	Emulsion	1997
Neoral [®] (cyclosporine soft gelatin capsules, USP modified)	Psoriasis	Emulsion	1997
Neoral [®] (cyclosporine oral solution, USP modified)	Psoriasis	Emulsion	1997
AmBisome [®] (amphotericin B liposome for injection)	Fungal infections	Liposome	1997
Celebrex [®] (celecoxib capsules)	Rheumatoid arthritis; Osteoarthritis; Ankylosing Spondylitis; Acute pain; Primary Dysmenorrhea	Nanocrystal	1998
Celebrex [®] (celecoxib capsules)	Familial adenomatous polyposis (FAP)	Nanocrystal	1999
Ferrlecit [®] (sodium ferric gluconate)	Iron deficiency anemia	Iron-Polymer Complex	1999

complex in sucrose injection)			
Visudyne [®] (verteporfin for injection)	Classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis	Liposome	2000
Venofer [®] (iron sucrose injection, USP)	Iron deficiency anemia	Iron-Polymer Complex	2000
Rapamune [®] (sirolimus tablets)	Prophylaxis of organ rejection in renal transplantation	Nanocrystal	2000
Restasis [®] (cyclosporine ophthalmic emulsion)	Ocular inflammation associated with keratoconjunctivitis sicca	Emulsion	2002
Emend [®] (aprepitant capsules)	Chemotherapy-induced and postoperative nausea and vomiting	Nanocrystal	2003
Oraqix [®] (lidocaine and prilocaine periodontal gel)	Local dental anesthetic	Emulsion	2003

Estrasorb [®] (estradiol topical emulsion)	Vasomotor symptoms due to menopause	Micelle	2003
TriCor [®] (fenofibrate tablets)	Hypercholesterolemia or mixed dyslipidemia; Hypertriglyceridemia	Nanocrystal	2004
Megace [®] ES (megestrol acetate oral suspension)	Anorexia, cachexia, or an unexplained significant weight loss in AIDS patients	Nanocrystal	2005
Abraxane [®] (paclitaxel protein-bound particles for injectable suspension)	Metastatic breast cancer; Locally advanced or metastatic non-small cell lung cancer (NSCLC); Metastatic adenocarcinoma of the pancreas	Drug-Protein Complex	2005
Penipro [®] SPF 20/RevitaLift [®] UV 20/Anthelios 20 [®] /UV Expert 20 [®] /Capital Soleil 20 [®] /UV Protective Suncare [®] (ecamsule sunscreen cream SPF 20)	Sunburn and skin damage	Nanocrystal	2006

Somatuline [®] Depot (lanreotide injection)	Acromegaly; Gastroenteropancreatic neuroendocrine tumors	Nanotube	2007
Durezol [®] (difluprednate ophthalmic emulsion)	Inflammation and pain associated with ocular surgery; Endogenous anterior uveitis	Emulsion	2008
Helioblock [®] SX SPF 40/UV Shield/ Anthelios 40 [®] /UV Expert 40 [®] /Capital Soleil 40 [®] (ecamsule sunscreen cream SPF 40)	Sunburn and skin damage	Nanocrystal	2008
Invega [®] Sustenna [®] (paliperidone palmitate extended- release injectable suspension)	Schizophrenia	Nanocrystal	2009
Feraheme [®] (ferumoxytol injection)	Iron deficiency anemia	Iron-Polymer Complex	2009
Marqibo [®] (vincristine)	Philadelphia chromosome-	Liposome	2012

sulfate liposome injection)	negative (Ph-) acute lymphoblastic leukemia (ALL)		
Ilevro [®] (nepafenac ophthalmic suspension)	Pain and inflammation associated with cataract surgery	Nanocrystal	2012
Injectafer [®] (ferric carboxymaltose injection)	Iron deficiency anemia	Iron-Polymer Complex	2013
Clinolipid [®] 20% (lipid injectable emulsion)	Parenteral nutrition	Emulsion	2013
Ryanodex [®] (dantrolene sodium for injectable suspension)	Malignant hyperthermia	Nanocrystal	2014
Onivyde [™] (irinotecan liposome injection)	Metastatic adenocarcinoma of the pancreas	Liposome	2015

**The nanotechnology terminologies do not represent any implication on CDER drug product*

labeling or naming conventions, and are used only to describe/interpret the type of structure of the nanomaterial in identified drug products for the purpose of this study.

Supplementary **Table 4.** CDER generic products (ANDAs) containing nanomaterials*

Grifulvin V [®] (griseofulvin oral suspension) microsize/Griseofulvin Oral Suspension (microsize)	Fungal infections	Nanocrystal	1984
Megestrol Acetate Tablets, USP	Palliative treatment of advanced carcinoma of the breast or endometrium	Nanocrystal	1988
Cyclosporine Capsules, USP (Modified)	Prophylaxis of organ rejection in kidney, liver, and heart transplantation; Rheumatoid arthritis; Psoriasis	Emulsion	2000
Gengraf [®] Capsules (cyclosporine capsules, USP [Modified])	Prophylaxis of organ rejection in kidney, liver, and heart transplantation; Rheumatoid arthritis; Psoriasis	Emulsion	2000
Gengraf [®] Oral Solution (cyclosporine	Prophylaxis of organ rejection in kidney, liver,	Emulsion	2000

oral solution, USP [Modified])	and heart transplantation; Rheumatoid arthritis; Psoriasis		
Cyclosporine Capsules, USP [Modified] (Soft Gelatin)	Prophylaxis of organ rejection in kidney, liver, and heart transplantation; Rheumatoid arthritis; Psoriasis	Emulsion	2000
Megestrol Acetate Oral Suspension, USP	Anorexia, cachexia, or an unexplained significant weight loss in patients with AIDS	Nanocrystal	2001
Cyclosporine Oral Solution, USP [Modified]	Prophylaxis of organ rejection in kidney, liver, and heart transplantation; Rheumatoid arthritis; Psoriasis	Emulsion	2001
Megestrol Acetate Oral Suspension USP	Anorexia, cachexia, or an unexplained significant weight loss in patients with AIDS	Nanocrystal	2002

Megestrol Acetate Oral Suspension, USP	Anorexia, cachexia, or an unexplained significant weight loss in patients with AIDS	Nanocrystal	2004
Cyclosporine Oral Solution, USP (Modified)	Prophylaxis of organ rejection in kidney, liver, and heart transplantation; Rheumatoid arthritis; Psoriasis	Emulsion	2005
Griseofulvin Oral Suspension, USP (microsize)	Fungal infections	Nanocrystal	2005
Cyclosporine Oral Solution USP Modified	Prophylaxis of organ rejection in kidney, liver, and heart transplantation; Rheumatoid arthritis; Psoriasis	Emulsion	2005
Cyclosporine Capsules USP Modified (Soft Gelatin Capsules)	Prophylaxis of organ rejection in kidney, liver, and heart transplantation; Rheumatoid arthritis; Psoriasis	Emulsion	2005

Griseofulvin Oral Suspension USP (microsize)	Fungal infections	Nanocrystal	2007
Griseofulvin Oral Suspension, USP (Microsize)	Fungal infections	Nanocrystal	2010
Sodium Ferric Gluconate Complex in Sucrose Injection	Iron deficiency anemia	Iron-Polymer Complex	2011
Fenofibrate Tablets USP	Hypercholesterolemia or mixed dyslipidemia; Hypertriglyceridemia	Nanocrystal	2011
Aprepitant Capsules	Chemotherapy-induced and postoperative nausea and vomiting	Nanocrystal	2012
Fenofibrate Tablets	Hypercholesterolemia or mixed dyslipidemia; Hypertriglyceridemia	Nanocrystal	2012
Griseofulvin Tablets, USP (microsize)	Fungal infections	Nanocrystal	2012
Ultramicrosize Griseofulvin Tablets, USP	Fungal infections	Nanocrystal	2012

Doxorubicin Hydrochloride Liposome Injection	Ovarian cancer; AIDS- related Kaposi's sarcoma; Multiple myeloma	Liposome	2013
Griseofulvin Tablets, USP (microsize)	Fungal infections	Nanocrystal	2013
Ultramicrosize Griseofulvin Tablets, USP	Fungal infections	Nanocrystal	2014
Megestrol Acetate Oral Suspension, USP	Anorexia, cachexia, or an unexplained significant weight loss in patients with AIDS	Nanocrystal	2014
Sirolimus Tablets	Prophylaxis of organ rejection in renal transplantation	Nanocrystal	2014

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Supplementary Table 5. Representative examples of particle size data as submitted by applicants

‘Mean and size distributions (D10, D50, D90)’

‘Mean’ only

‘D10, D50, or D90’ only

‘More than 80 nm’

‘Not more than 350 nm’

‘0.6-7 μm not less than 97.0%’

‘Not less than 97% of particles less than 1.2 μm ’

‘ $\text{D50} \leq 1.5 \mu\text{m}$ ’

‘Mean particle size < 1000 nm’

‘Mean particle size < 150 nm and D90 < 250 nm’

‘Mean diameter < 200 nm’

Zave