Complex Drug Products Containing Nanomaterials

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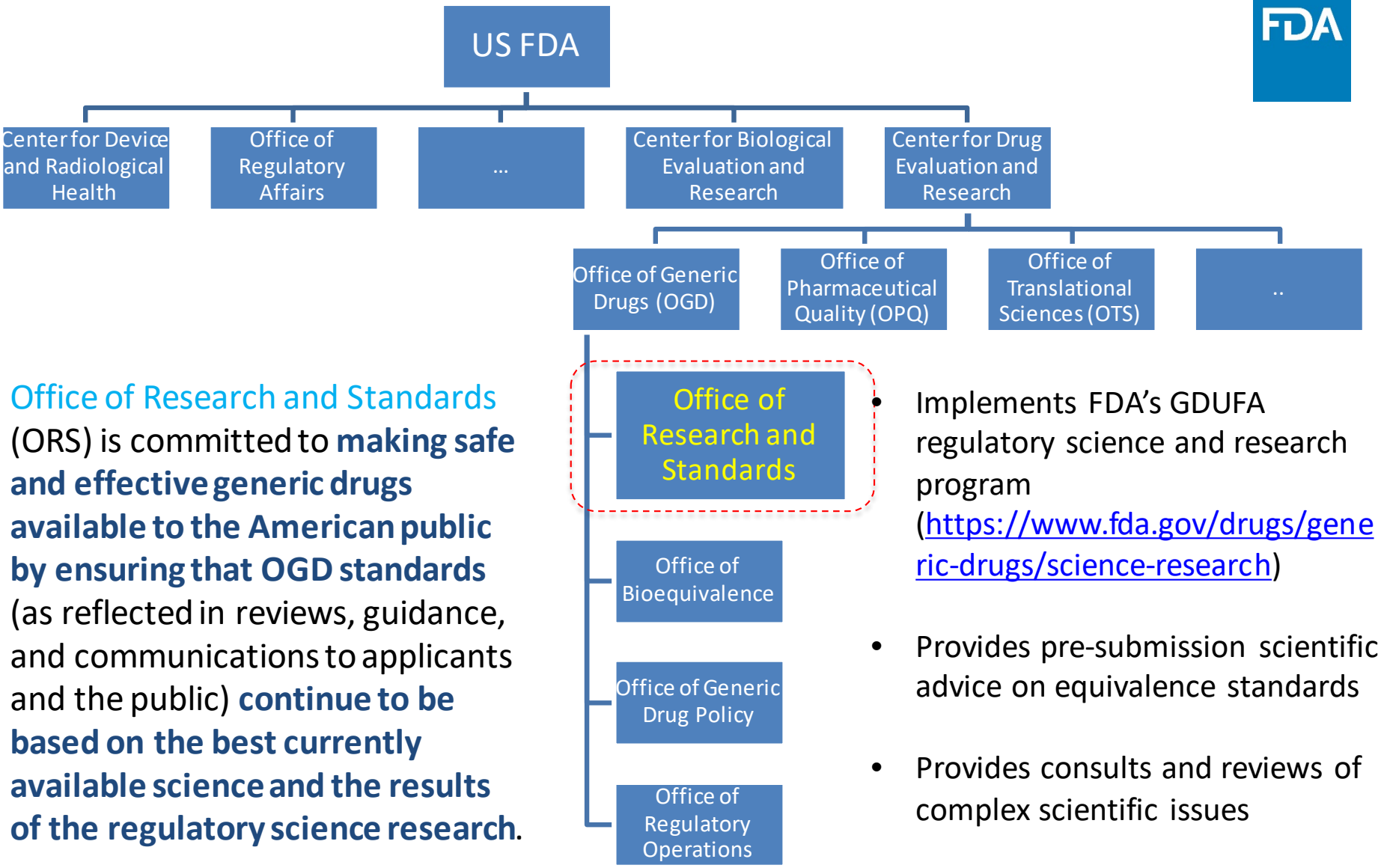


Office of Research and Standards (ORS) is committed to **making safe and effective generic drugs available to the American public by ensuring that OGD standards** (as reflected in reviews, guidance, and communications to applicants and the public) **continue to be based on the best currently available science and the results of the regulatory science research**.

- Implements FDA's GDUFA regulatory science and research program (https://www.fda.gov/drugs/generic-drugs/science-research)
- Provides pre-submission scientific advice on equivalence standards
- Provides consults and reviews of complex scientific issues
- Ensures therapeutic equivalence of approved generic drugs

GDUFA: Generic Drug User Fee Amendments

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.

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

Lionberger R. Innovation for Generic Drugs: Science and Research Under the Generic Drug User Fee Amendments of 2012, *Clinical pharmacology & therapeutics*, 2019, Vol.105(4), p.878-885

Nanomaterials (U.S. FDA)

- 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 1–100 nm), and
- 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

Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

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**

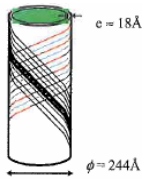
Long-Acting Injectable (LAI) Products

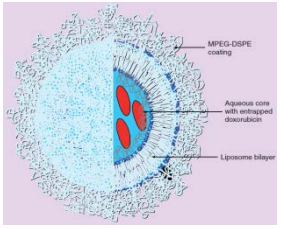
- Suspensions (e.g., aripiprazole LAI suspension)
- Multivesicular liposomes (e.g., bupivacaine liposomes)
- Biodegradable implants/inserts (e.g., leuprolide acetate)
- Microspheres (e.g., risperidone)

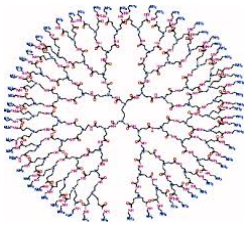
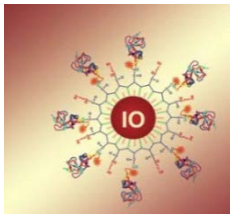
Limited Generics Available for Complex Products Containing Nanomaterials

Platform	Examples			
	Name	New Drug Application (NDA) Approval	Indication	1st Abbreviated New Drug Application (ANDA) Approval
Liposome	DOXIL® (Doxorubicin)	1995	Cancer	2013, 3 generics approved
Inorganic nanoparticle	FERRLECIT® (Sodium ferric gluconate complex)	1999	Anemia	2011, 1 generics approved
Protein nanoparticle	ABRAXANE® (Paclitaxel)	2005	Cancer	None
Emulsion	RESTASIS® (Cyclosporine)	2002	To increase tear production	None
Lipid complex	AMPHOTEC® (Amphotericin B)	1996	Invasive aspergillosis	None
Nanotube	SOMATULINE DEPOT® (Lanreotide acetate)	2007	Acromegaly	None
Micelle	TAXOTERE®(Docetaxel)	1996	Cancer	None

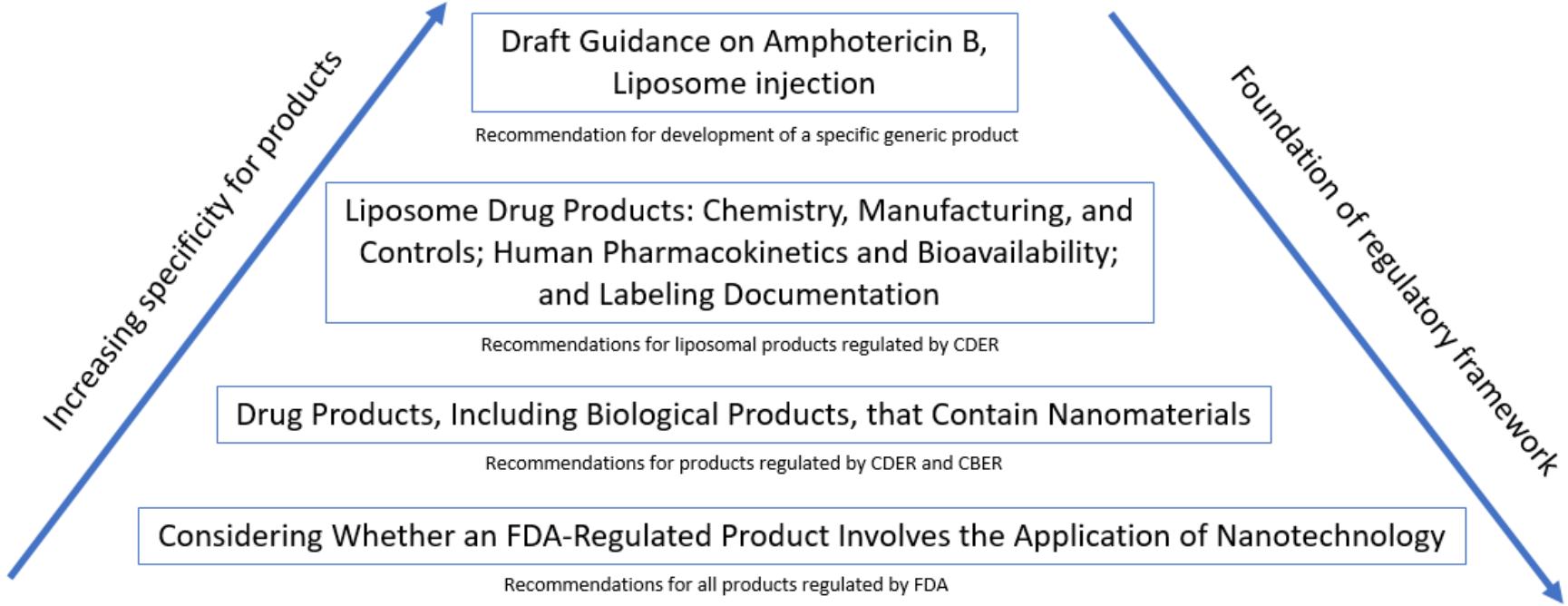
(Not a complete list)



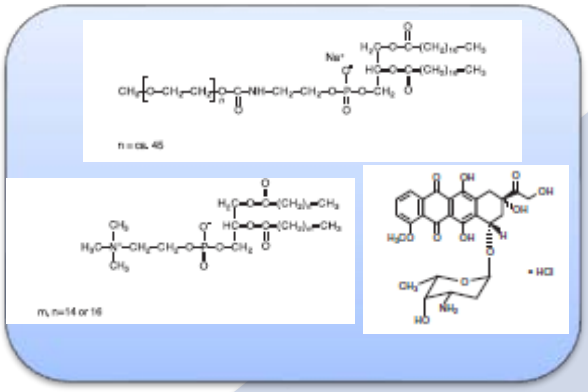
U.S. FDA Guidance Related to Nanotechnology Products

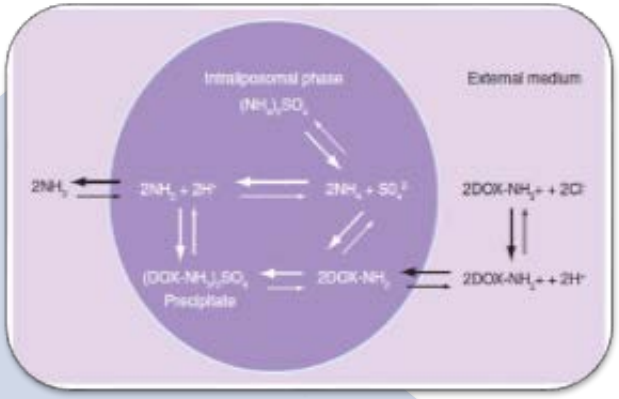


Vlieger, J, et al. Report of the AAPS Guidance Forum on the FDA Draft Guidance for Industry: Drug Products, Including Biological Products, that Contain Nanomaterials. The AAPS Journal (2019) 21: 56

U.S. FDA Product-Specific Guidance for Doxorubincin HCl Liposomes

Qualitative (Q1) and Quantitative (Q2) sameness

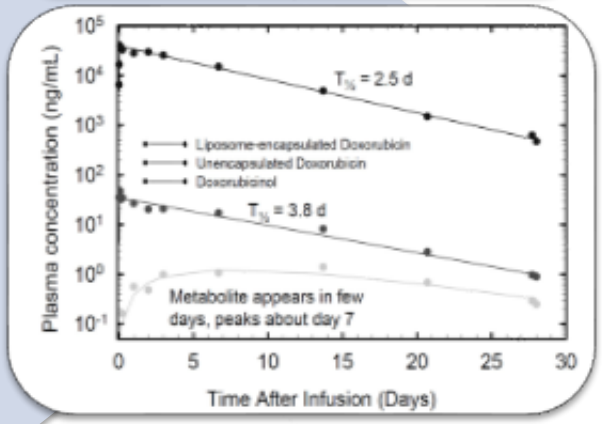




Same remote loading manufacturing process

Characteristics	Analytical methods
Lipid composition (e.g., lipid quantities, free and encapsulated drug, internal and total sulfate conc., histidine and sucrose conc., drug to lipid ratio)	HPLC
State of encapsulated drug	Cryo TEM, XRD
Internal environment (e.g., pH, volume)	NMR, ESR, and others
Liposome morphology & number of lamella	TEM, Cryo-TEM, AFM
Lipid bilayer phase transition	DSC
Liposome size distribution	DLS, EM
Grafted PEG at the liposome surface	NMR
Surface charge	Zeta potential measurement
In vitro drug leakage	Multiple release conditions

Equivalent physico-chemical characteristics



Equivalent free and liposome associated drug exposure

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

Jiang W, Lionberger R, Yu L, In vitro and in vivo characterizations of PEGlyated liposome doxorubicin. Bioanalysis. 2011 Feb;3(3):333-44
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf

Continued Development of Product-Specific Guidances

FDA published product-specific guidances for nanotechnology drug products

- doxorubicin HCl liposome injection
- verteporfin liposome injection
- amphotericin B liposome injection
- daunorubicin liposome injection
- sodium ferric gluconate injection
- ferumoxytol injection
- iron sucrose injection
- cyclosporine emulsion
- lanreotide acetate injection
- paclitaxel albumin-bound particles for injectable suspension

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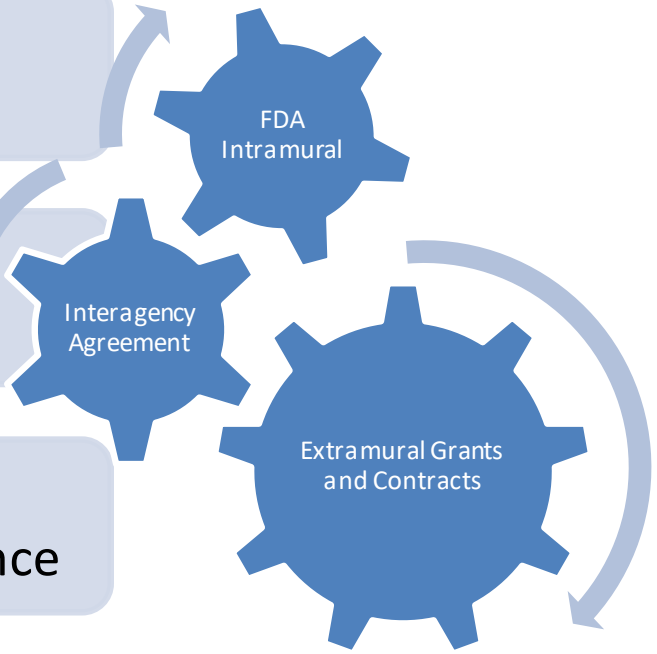
(Not a complete list)

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

CDER Nanotechnology Research Focus

Quality	• Characterization • Manufacturing
Safety	• Drug exposure • Toxicity
Equivalence	• **In vitro characterization** • In vivo pharmacokinetics
Post-market surveillance	• Lab investigation • Passive and active surveillance



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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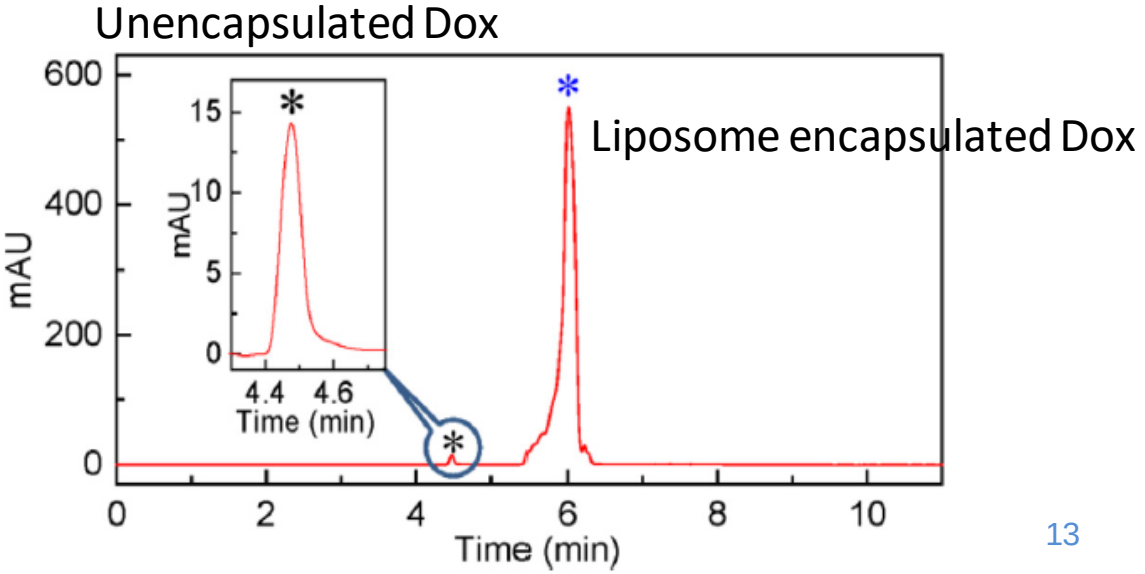
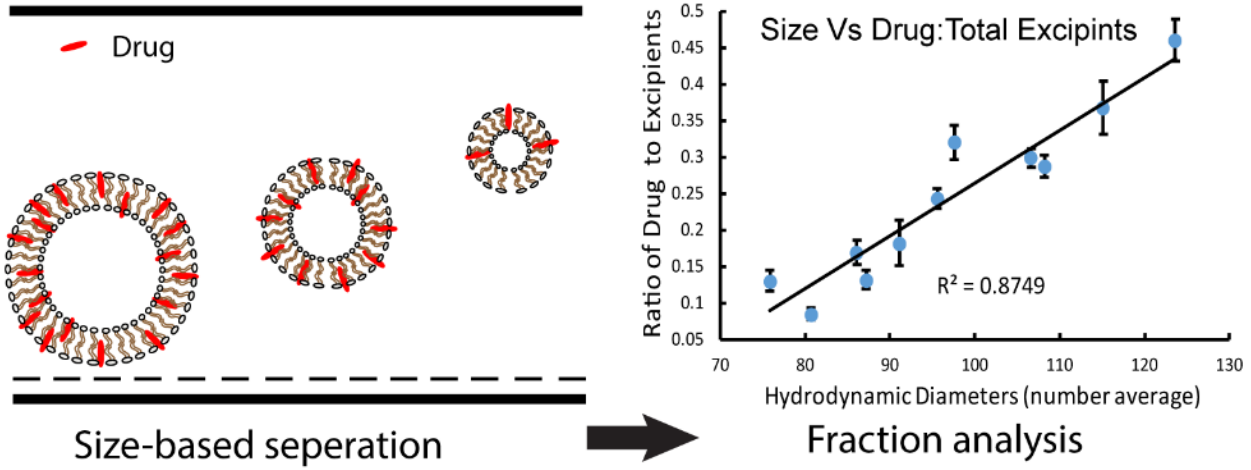


Quantification of Lipid Excipients and Active Pharmaceutical Ingredients (APIs) in Liposomes



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

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CDER Nanotechnology Research Resources

CDER Nanotechnology Program

https://www.fda.gov/science-research/nanotechnology-programs-fda/center-drug-evaluation-and-research-nanotechnology-programs

GDUFA Regulatory Science Report and Guidance

https://www.fda.gov/drugs/generic-drugs/generic-drug-research-related-guidances-reports

Continued Efforts to Promote Harmonization on Nanomedicine Evaluation Criteria

U.S. FDA Doxorubicin HCl liposomes Product-Specific Guidance (Recommended 2010, most recent revision 2018)

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

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

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

IPRP Nanomedicine Working Group Liposome Survey

- Survey Objectives
  - Capture the regulatory progress for liposome products from the expanded International Pharmaceutical Regulator Programme (IPRP) members
  - Identify the needs of both research and standard development
  - Enhance the potential for harmonization of regulatory requirements

- Survey for both regulatory agencies and non-regulatory stakeholders

- Survey out on 07/02/20 and response due 09/01/20

- Analysis ongoing

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

Summary

- Non-oral nanomaterials are considered complex drug products, and there are limited number of generics available for these products.

- U.S. FDA publishes guidances and conducts regulatory research to support nanotechnology drug product development.

- International collaborations are needed to facilitate research and standards development, as well as harmonization of regulatory recommendations, for nanotechnology drug products.

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- Office of Regulatory Affairs