

# Quality Considerations and Control for Drug Products Containing Nanomaterials

**From Doxil to Onpattro**

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CDER | US FDA

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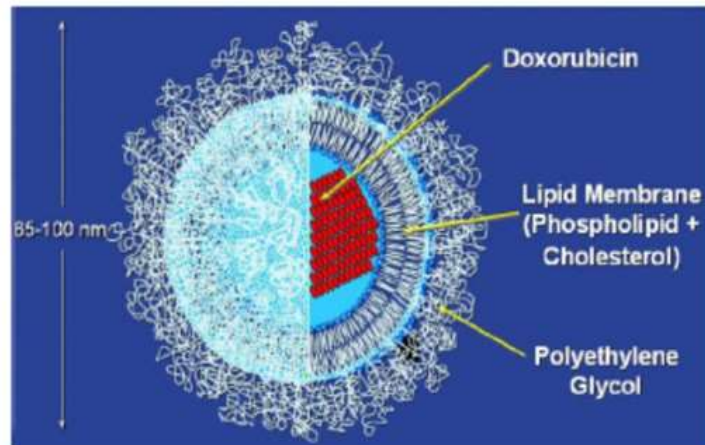
## Doxil®

API: small molecule  
(Doxorubicin Hydrochloride)

**Drug carrier: Liposomes**

Indication: Ovarian Cancer; AIDS-related Kaposi's Sarcoma; Multiple Myeloma

**Approval date: 11/17/1995**



Adapted from: Barenholz Y. Doxil® — the first FDA-approved Nano-drug: Lessons learned. Journal of Controlled Release 2012; 16:117–134.

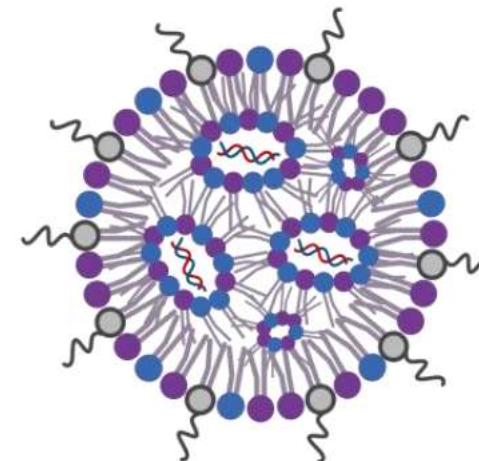
## Onpattro®

API: siRNA  
(Patisiran)

**Drug carrier: Lipid nanoparticles**

Indication: polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults

**Approval date: 08/10/2018**



Adapted from: Thi, T. T. H. et al Lipid-Based Nanoparticles in the Clinic and Clinical Trials: From Cancer Nanomedicine to COVID-19 Vaccines. Vaccines April 2021.

# Overview

- **liposome drug products – a story of success**
- **What do we learn?**
- **Lipid Nanoparticle Drug Products – a new legend**
- **Where are we going?**

# FDA Approved Liposome Drug Products

Trade name	Active Ingredient	Indication	Route	Initial Approval Date
<b>Doxil</b>	Doxorubicin HCl	cancer	Intravenous	11/17/1995
<b>DaunoXome*</b>	Daunorubicin Citrate	cancer	Intravenous	04/08/1996
<b>AmBisome</b>	Amphotericin B	infections	Intravenous	08/11/1997
<b>DepoCyt*</b>	Cytarabine	cancer	Intrathecal	04/01/1999
<b>Visudyne</b>	Verteporfin	photosensitizer	Intravenous	04/12/2000
<b>Definity</b>	Perflutren	ultrasound contrast agent	Intravenous	07/31/2001
<b>DepoDur*</b>	Morphine Sulfate	pain following major surgery	Epidural	05/18/2004
<b>Exparel</b>	Bupivacaine	analgesia	Intravenous	10/28/2011
<b>Marqibo</b>	Vincristine Sulfate	cancer	Intravenous	08/09/2012
<b>Onivyde</b>	Irinotecan HCl	cancer	Intravenous	10/22/2015
<b>Vyxeos</b>	Daunorubicin and Cytarabine	cancer	Intravenous	08/03/2017
<b>Arikayce Kit</b>	Amikacin Sulfate	Lung disease	Oral inhalation	09/28/2018

\* Discontinued



# Generic Liposome Drug Products Development

Product Specific Guidance (PSG) developed by FDA  
&  
FDA approved Generic Liposome Drug Products

Drug Product	PSG History	Approved ANDAs
Doxorubicin Hydrochloride Liposome injection (Doxil)	Recommended Feb 2010; Revised Nov 2013, Dec 2014, Apr 2017, Sept 2018	5 ANDAs approved between 2013 to 2022
Amphotericin B liposome injection (AmbiSome)	Recommended Apr 2014; Revised Jan 2016, Aug 2020	2 ANDA approved in between 2021 and 2022
Verteporfin for Injection (Visudyne)	Recommended Apr 2014	
Bupivacaine Liposome Injectable Suspension (Exparel)	Recommended Feb 2018	
Perflutren Lipid Microsphere Injectable Suspension (Definity)	Recommended Sept 2018	
Irinotecan Hydrochloride Liposome Injection	Recommended Feb 2022	
Cytarabine and Daunorubicin Liposome for Injection	Recommended Aug 2022	

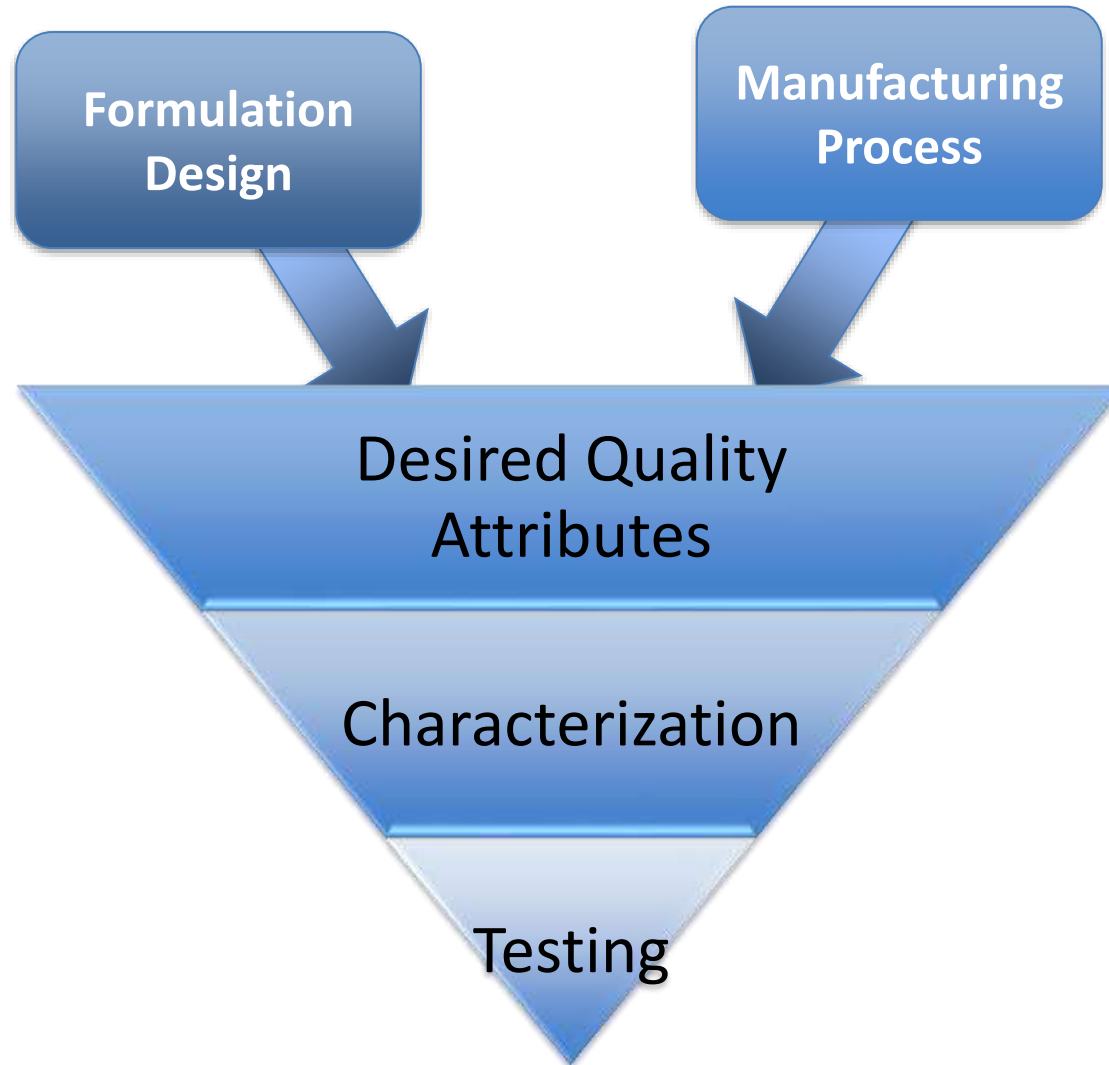


# Other Relevant Guidance

- [Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation](#)
- [Drug Products, Including Biological Products, that Contain Nanomaterials](#)

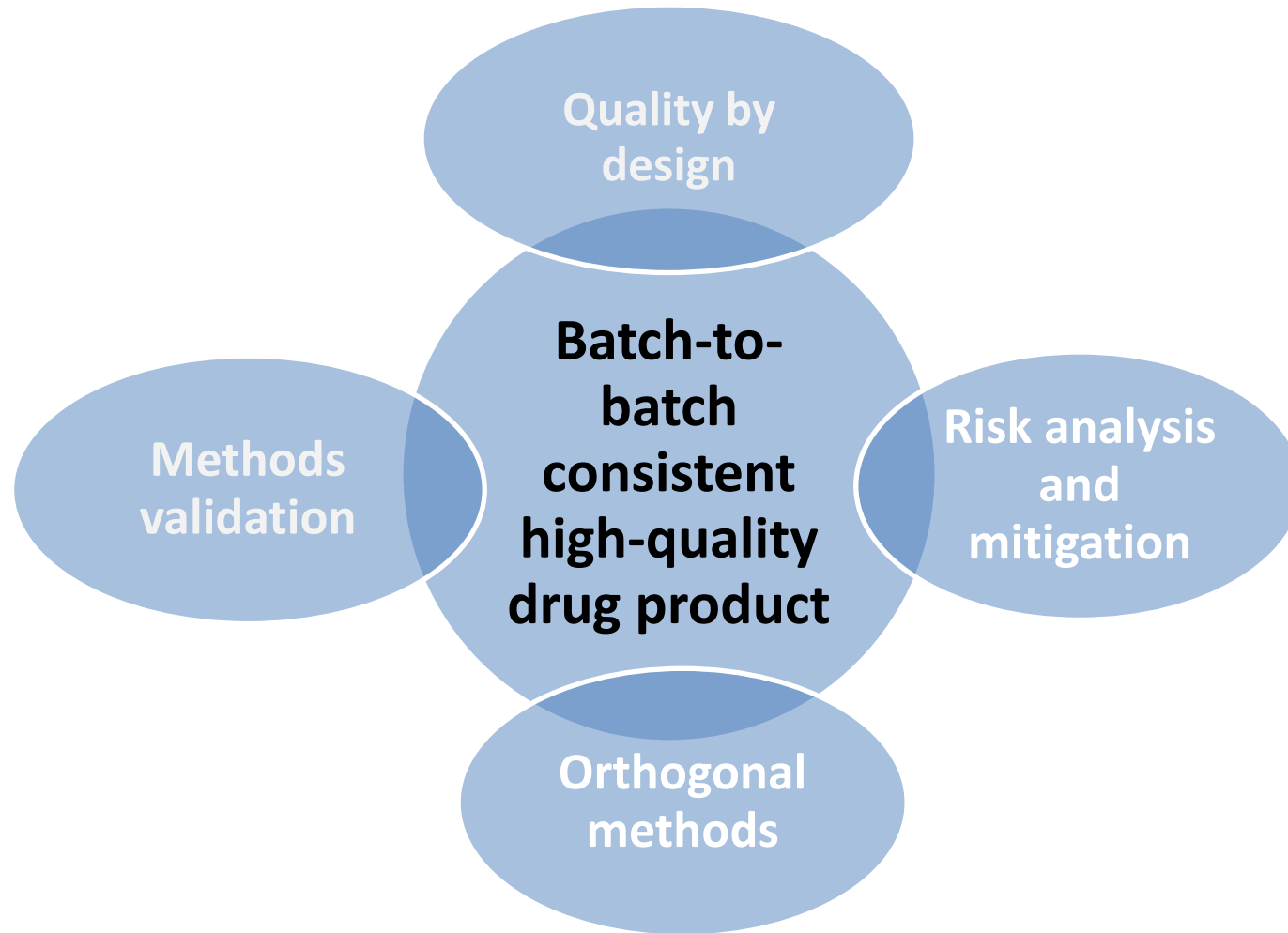
# What Do We learn?

- quality perspectives



# What Do We learn?

- quality perspectives





# Lipid Nanoparticles

**“The origins of LNP systems used for genetic drugs lie in the development of liposomal drug delivery systems for small molecule drugs”**

- Cullis, P.R. and M.J. Hope, Lipid Nanoparticle Systems for Enabling Gene Therapies. Mol Ther, 2017. 25(7): p. 1467-1475.

# From Doxil® to Onpattro®

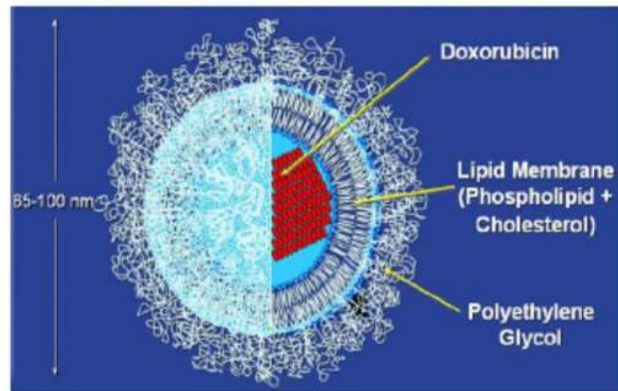


- ***Desired profiles for delivery genetic drugs: - lessons learned from liposome drug products***
  - a size range of 100 nm or less
  - high encapsulation efficacy
  - circulation longevity
  - robust, scalable manufacturing processes
  - stability
- ***Specific requirements for delivery of siRNA***
  - Ionizable cationic lipids -facilitate association and encapsulation;
  - near-neutral charge on the external membrane surface;
  - dissociation of PEG from LNP in vivo quickly

# From Doxil® to Onpattro® -Formulation Development



## Doxil®



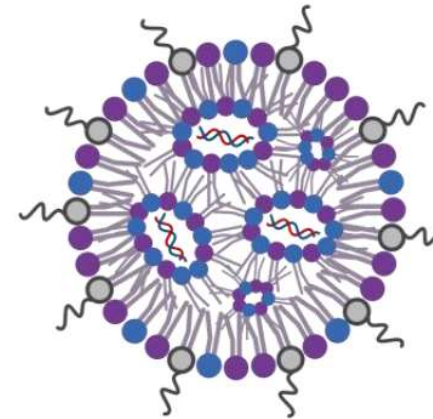
Dosage form: Liposome Injection

Lipids: HSPC

Cholesterol

MPEG 2000-DSPE

## Onpattro®



Dosage form: Lipid Complex Injection

Lipids: HSPC

Cholesterol

PEG 2000-C-DMG

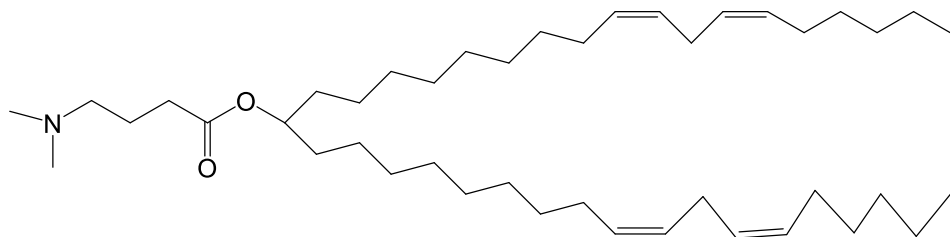
Dlin-MC3-DMA

# Onpattro – Lipid Selection



## Ionizable cationic lipid - Dlin-MC3-DMA

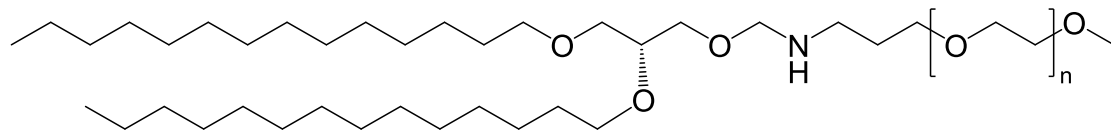
Chemical name: (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4- (dimethylamino)butanoate



- **Optimized Pka to ~6.4: positively charged at an acidic pH but neutral in the blood;**
- **Encapsulation at acidic pH**
- **Neutral surface charge at physiological pH**

## PEG lipid - PEG<sub>2000</sub>-C-DMG

(R)-2,3-bis(tetradecyloxy)propyl 1 (methoxypoly(ethylene glycol)2000)propyl carbamate

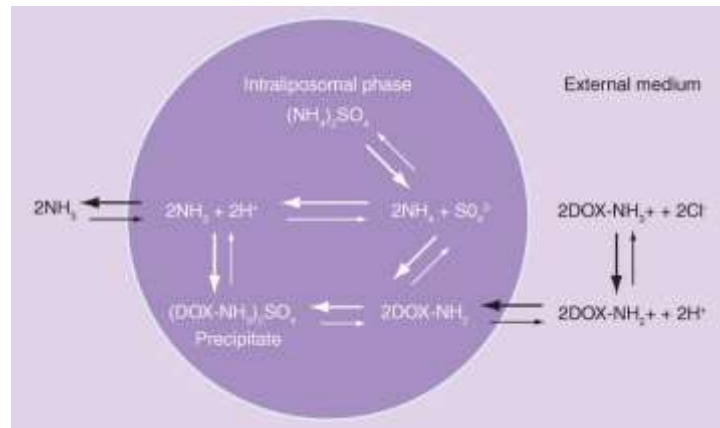


- **Stabilize the LNP particle**
- **Control the particle size**
- **C14 alkyl chain – fast dissociation in vivo**

# From Doxil® to Onpattro® -High Encapsulation Efficiency

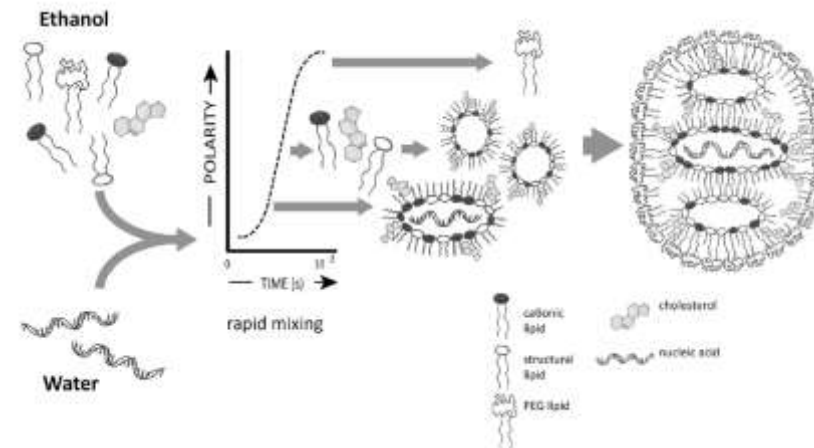
## Doxil®

Active drug loading by ion gradient method



## Onpattro®

- Ionizable cationic lipid complexes with the nucleic acids in acidic media (pH~4) by electrostatic interaction
- Ethanol loading process



Jiang, W, Lionberger R. and Yu L.X., In vitro and in vivo characterizations of PEGylated liposomal doxorubicin Bioanalysis. 2011 Feb;3(3):333-44.  
Cullis, P.R. and M.J. Hope, Lipid Nanoparticle Systems for Enabling Gene Therapies. Mol Ther, 2017. 25(7): p. 1467-1475.

# From Doxil® to Onpattro® -Manufacturing Evolution



- **Extrusion method (Doxil)**
- **Homogenization**
- **Ethanol loading method (Onpattro)**

T-tube mixing process was developed where lipids dissolved in ethanol were rapidly mixed with oligonucleotides in an aqueous buffer resulting in efficient loading of nucleic acid polymers into small (diameter <100 nm) LNP systems.

Cullis, P.R. and M.J. Hope, Lipid Nanoparticle Systems for Enabling Gene Therapies. Mol Ther, 2017. 25(7): p. 1467-1475.

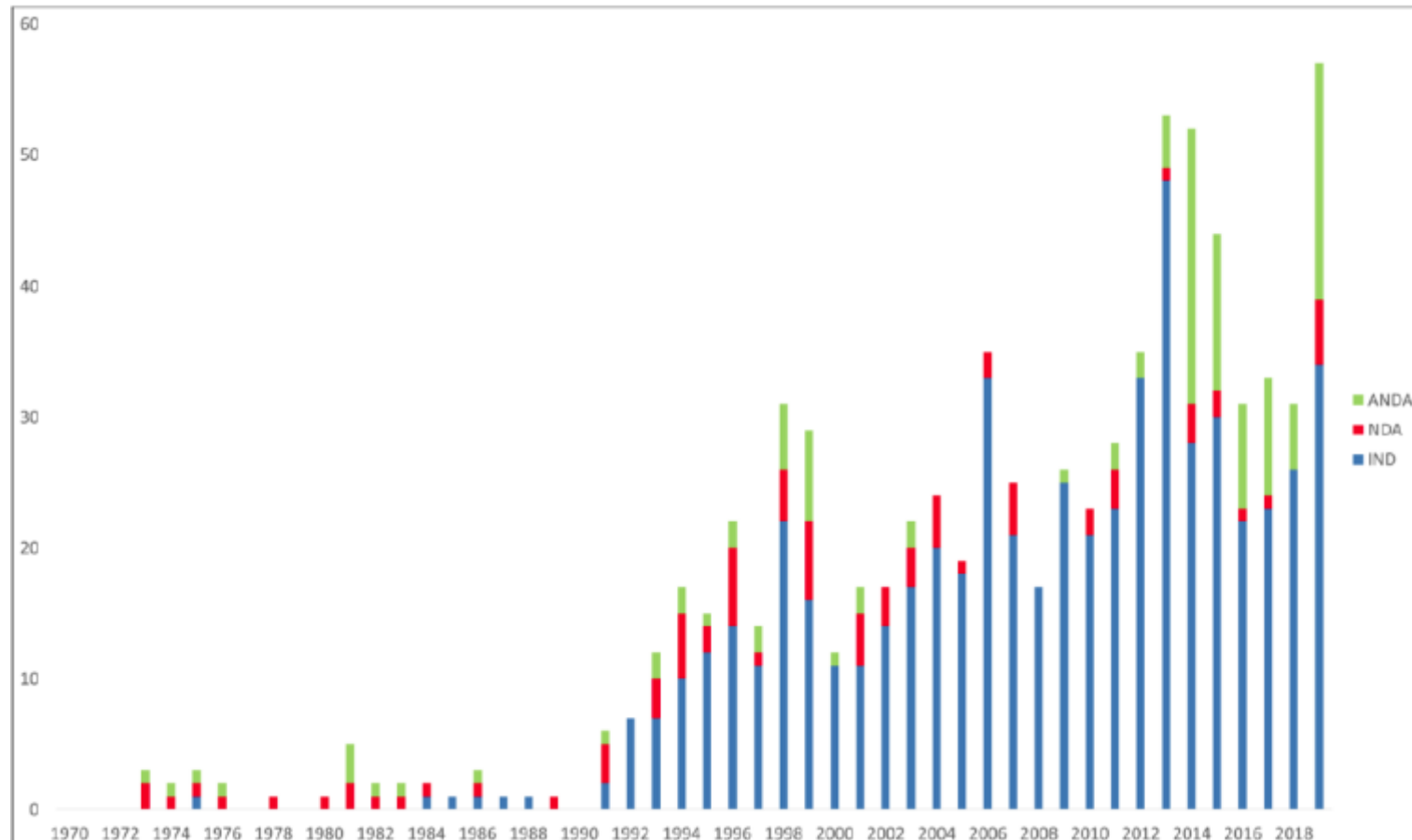
# From Doxil® to Onpattro® - Characterization and Testing



- Morphology – Cryo-TEM
- Surface charge
- Particle size and size distribution - DLS
- Encapsulation efficiency
- In-Vitro Release

# Where Are We Going

- Submissions to the US FDA of Drug Products Containing Nanomaterials





# Closing Thought

## *a science-based, product-focused regulatory policy:*

- Design and intent of nanomaterial (QbD)
- Risk-based approach
- Identify process risks and control strategy
- Characterization is key through development - Adequacy of analytical methods; Sampling strategy; Orthogonal methods
- Encourage industry to consult with the Agency early in product development (pIND and PDEV)



# Acknowledgement

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