Quality Considerations and Control for Drug Products Containing Nanomaterials

From Doxil to Onpattro

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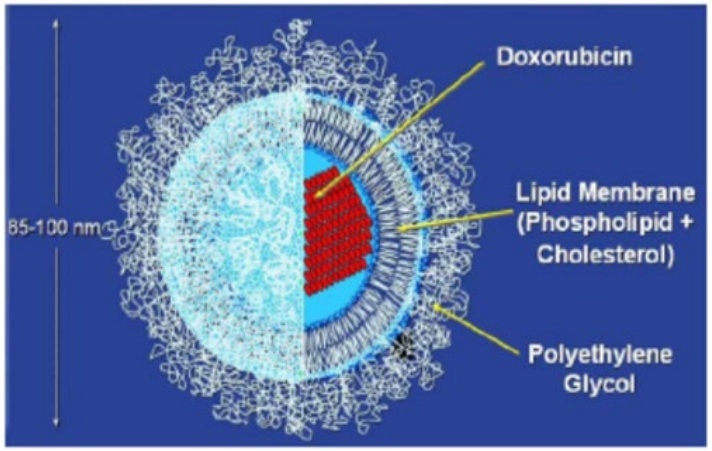
Doxil®

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.

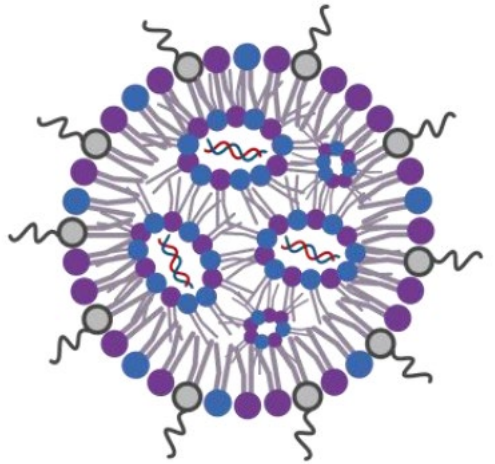
Onpattro®

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
Doxil	Doxorubicin HCl	cancer	Intravenous	11/17/1995
DaunoXome*	Daunorubicin Citrate	cancer	Intravenous	04/08/1996
AmBisome	Amphotericin B	infections	Intravenous	08/11/1997
DepoCyt*	Cytarabine	cancer	Intrathecal	04/01/1999
Visudyne	Verteporfin	photosensitizer	Intravenous	04/12/2000
Definity	Perflutren	ultrasound contrast agent	Intravenous	07/31/2001
DepoDur*	Morphine Sulfate	pain following major surgery	Epidural	05/18/2004
Exparel	Bupivacaine	analgesia	Intravenous	10/28/2011
Marqibo	Vincristine Sulfate	cancer	Intravenous	08/09/2012
Onivyde	Irinotecan HCl	cancer	Intravenous	10/22/2015
Vyxeos	Daunorubicin and Cytarabine	cancer	Intravenous	08/03/2017
Arikayce Kit	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	

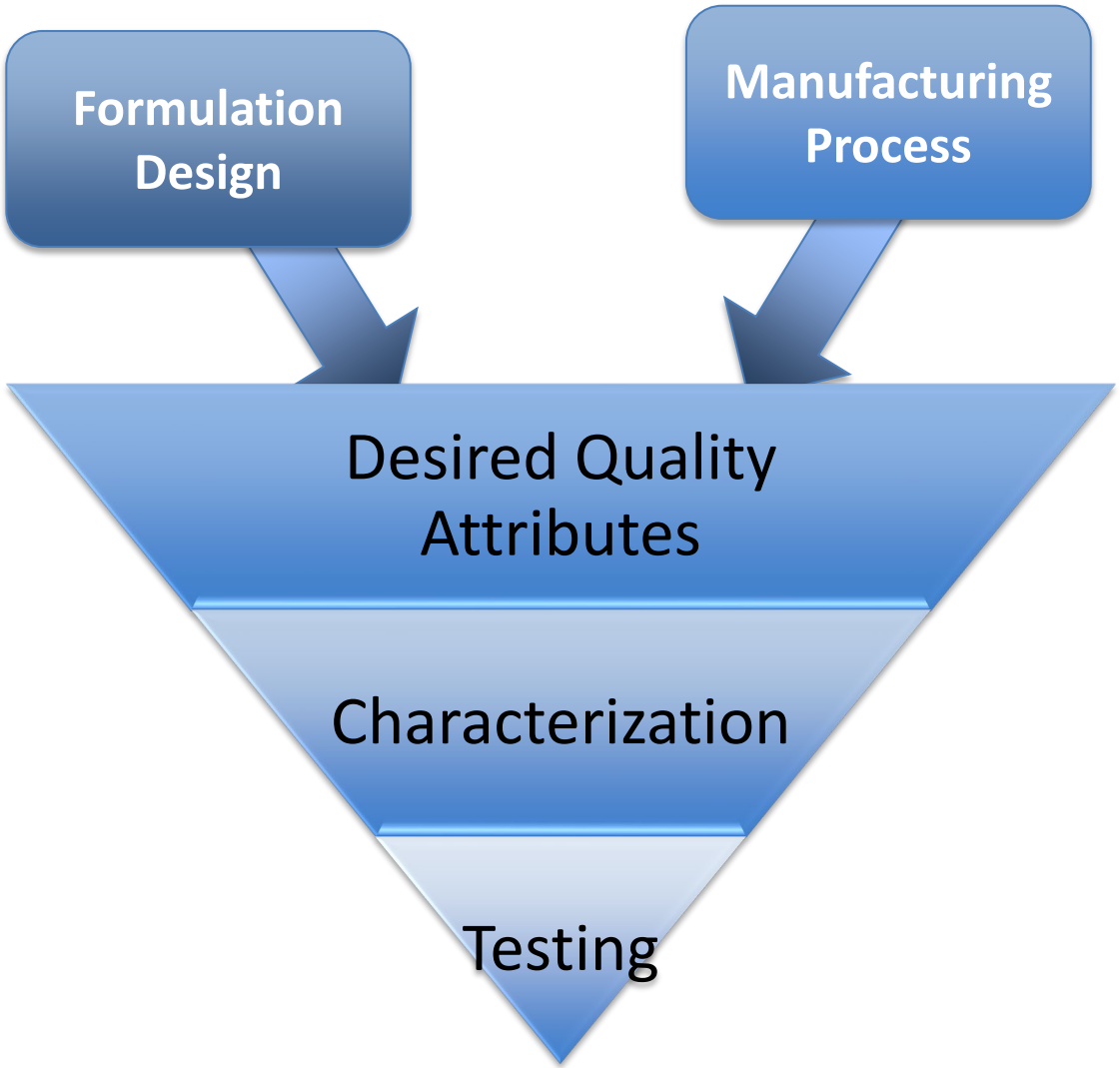
Other Relevant Guidance

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

- Drug Products, Including Biological Products, that Contain Nanomaterials

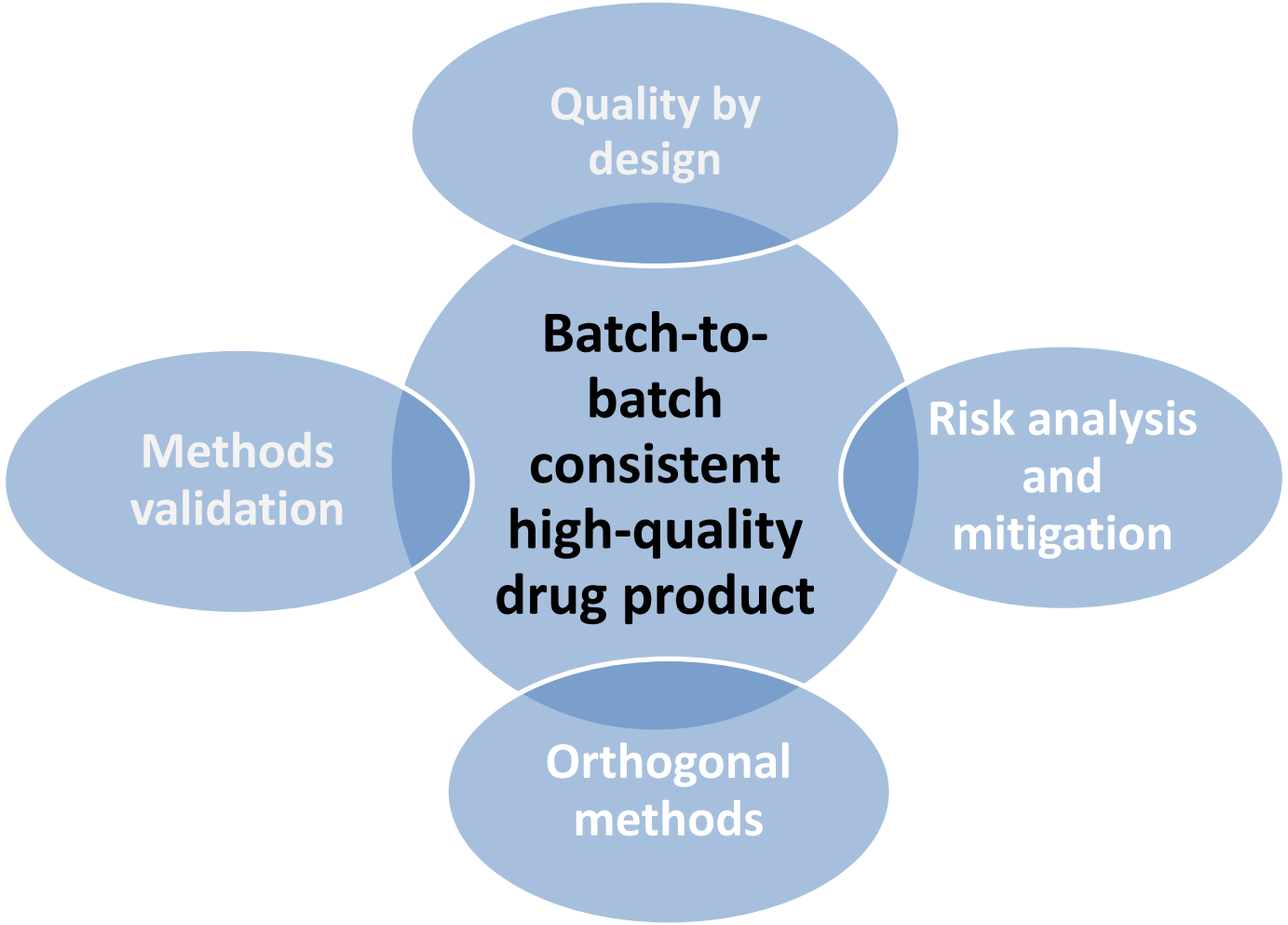
What Do We learn?

- 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***

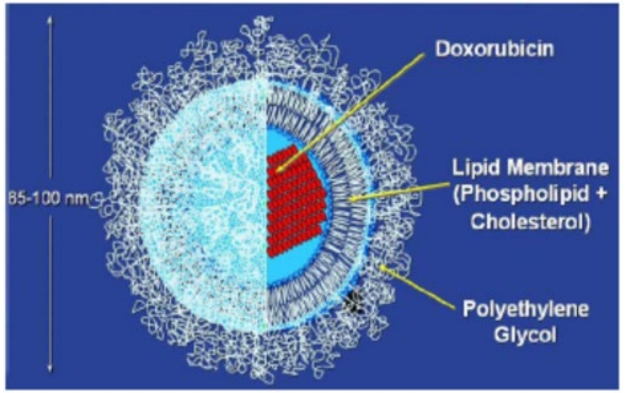
  - a size range of 100 nm or less
  - high encapsulation efficacy
  - circulation longevity
  - robust, scalable manufacturing processes
  - stability

- ***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

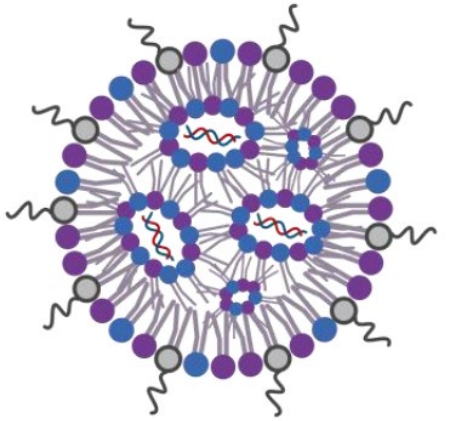
From Doxil® to Onpattro®
-Formulation Development

Doxil®



Dosage form: Liposome Injection
Lipids: HSPC
Cholesterol
MPEG 2000-DSPE

Onpattro®

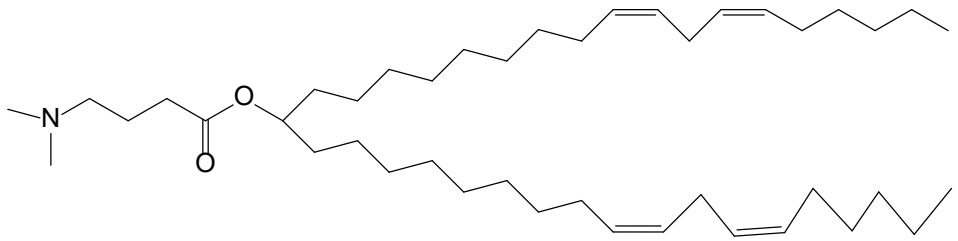


Dosage form: Lipid Complex Injection
Lipids: HSPC
Cholesterol
PEG 2000-C-DMG
Dlin-MC3-DMA

Onpattro – Lipid Selection

Ionizable cationic lipid - Dlin-MC3-DMA

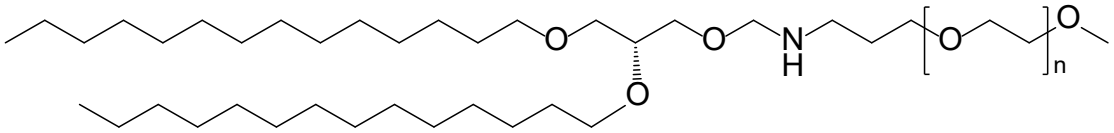
Chemical name: (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4- (dimethylamino)butanoate



- **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 - PEG2000-C-DMG

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



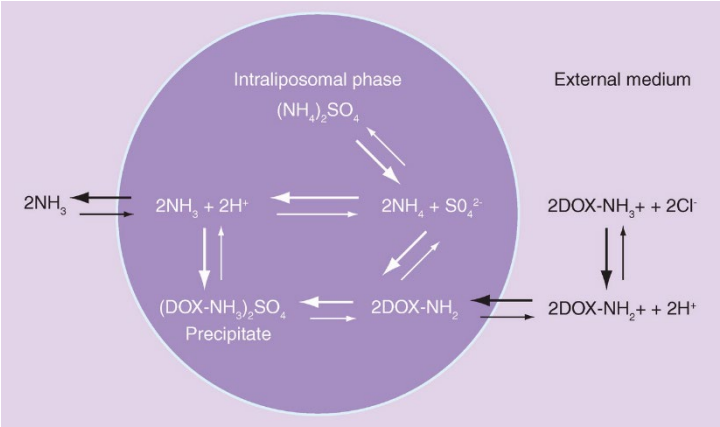
- **Stabilize the LNP particle**
- **Control the particle size**
- **C14 alkyl chain – fast dissociation in vivo**

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.

From Doxil® to Onpattro®
-High Encapsulation Efficiency

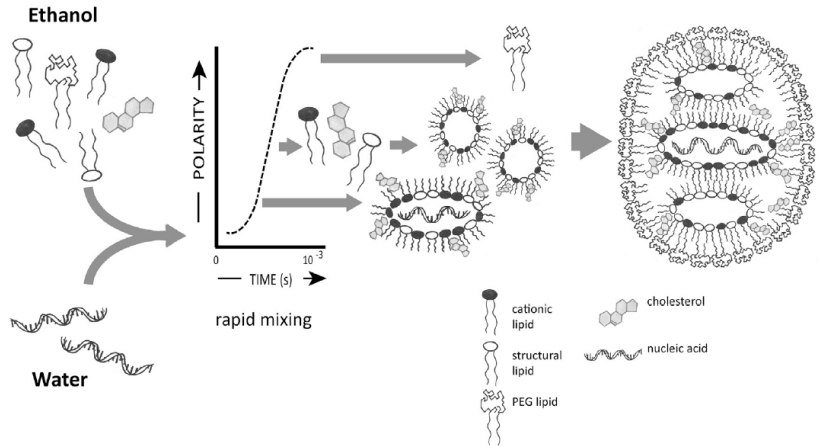
Doxil®

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.

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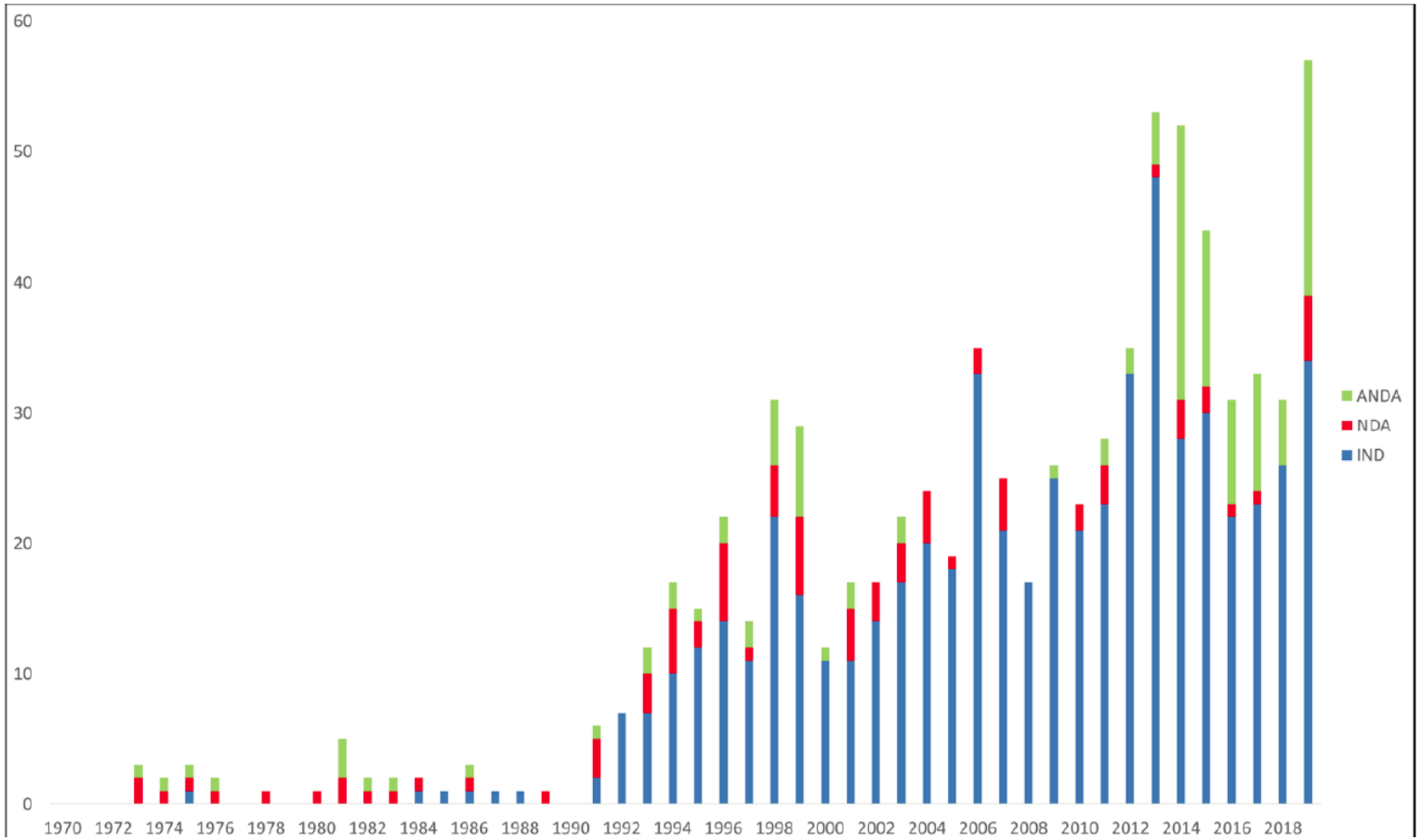
From Doxil® to Onpattro®
- Characterization and Testing

- 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



Nanotechnology Task Force Report 2020

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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Thank you!