Biomaterials and Drugs - Generic Drugs with Biomaterial Components: Impact on Drug Delivery & Drug Complexity

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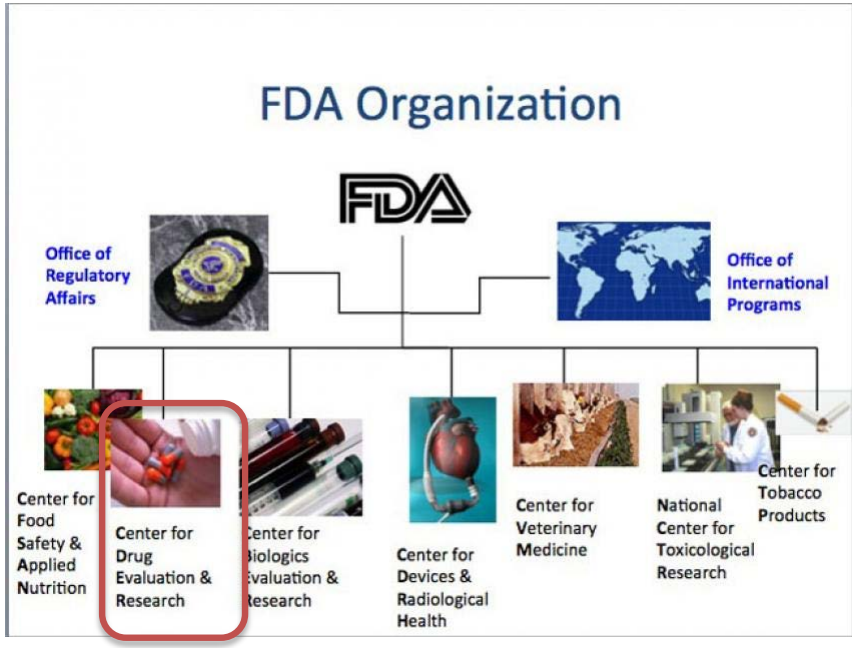
Committee Roundtable on Biomedical Engineering Materials and Applications, National Academies

FDA Campus


FDA
U.S. Department of Health and Human Services
Food and Drug Administration


FDA Organization
FDA
Office of Regulatory Affairs
Office of International Programs
Center for Food Safety & Applied Nutrition
Center for Drug Evaluation & Research
Center for Biologics Evaluation & Research
Center for Devices & Radiological Health
Center for Veterinary Medicine
National Center for Toxicological Research
Center for Tobacco Products

Office of Generic Drugs (OGD)

- Located in the Center for Drug Evaluation and Research
- Four Sub-Offices: Bioequivalence, Regulatory Operations, Generic Drug Policy, Research and Standards
- Office of Research and Standards (ORS) – leads the implementation of regulatory science commitments and translates research results into standards for safe, effective, and equivalent generic drugs.

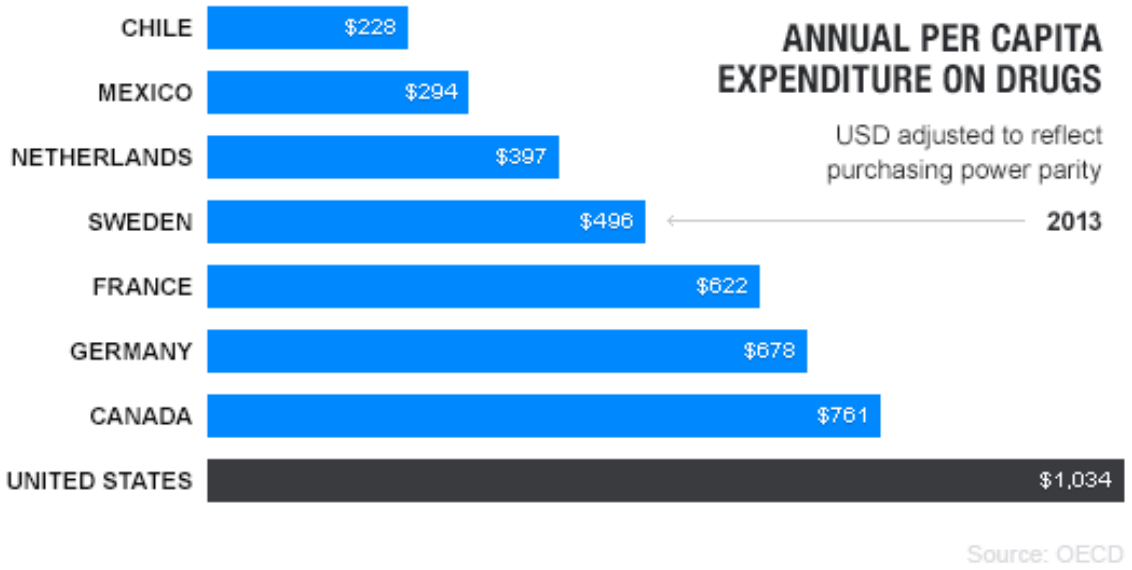
Generic Drugs:

- Are duplicates of brand-name drugs
- Are the same as those brand name drugs in active ingredients, dosage form, strength, route of administration, quality, performance characteristics, safety, efficacy, and intended use.

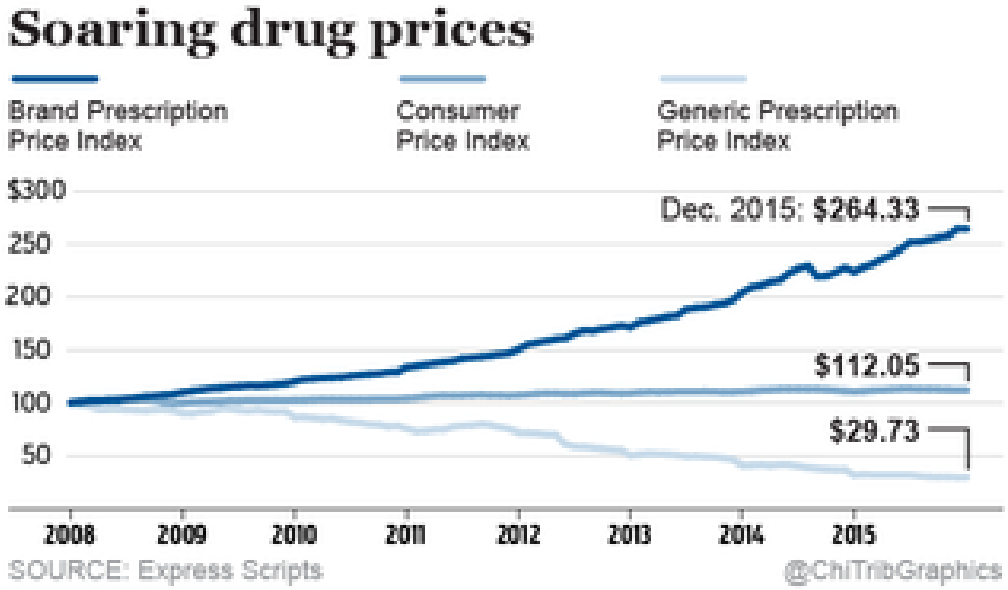
From FDA website – Understanding Generic Drugs
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm

Introduction to Generic Drugs

- Each ANDA (Abbreviated New Drug Application) relies on a reference listed drug (RLD)
- Generic drugs cost less to develop because sponsors do not repeat the safety and efficacy studies used to approve the RLD.

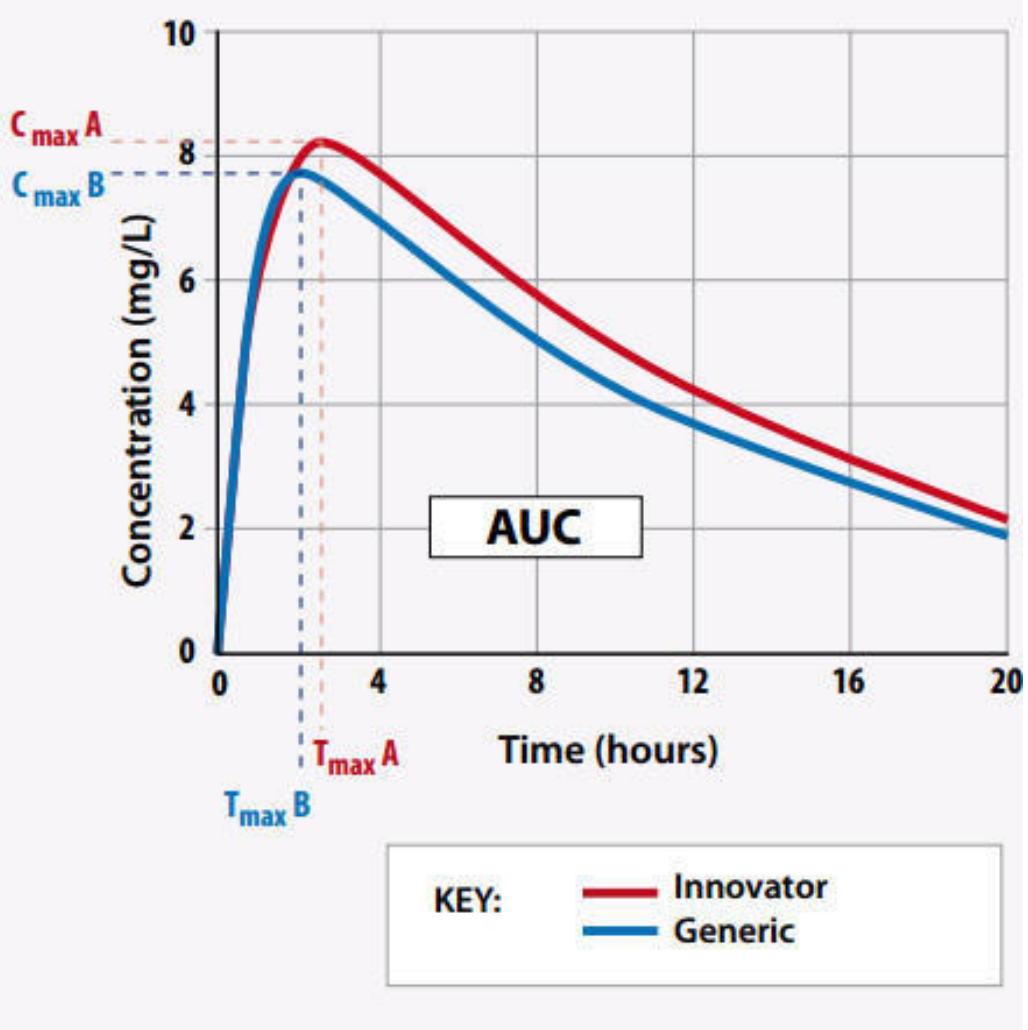


Fortune, 2015



Chicago Tribune, 2016

Bioequivalence Determinations



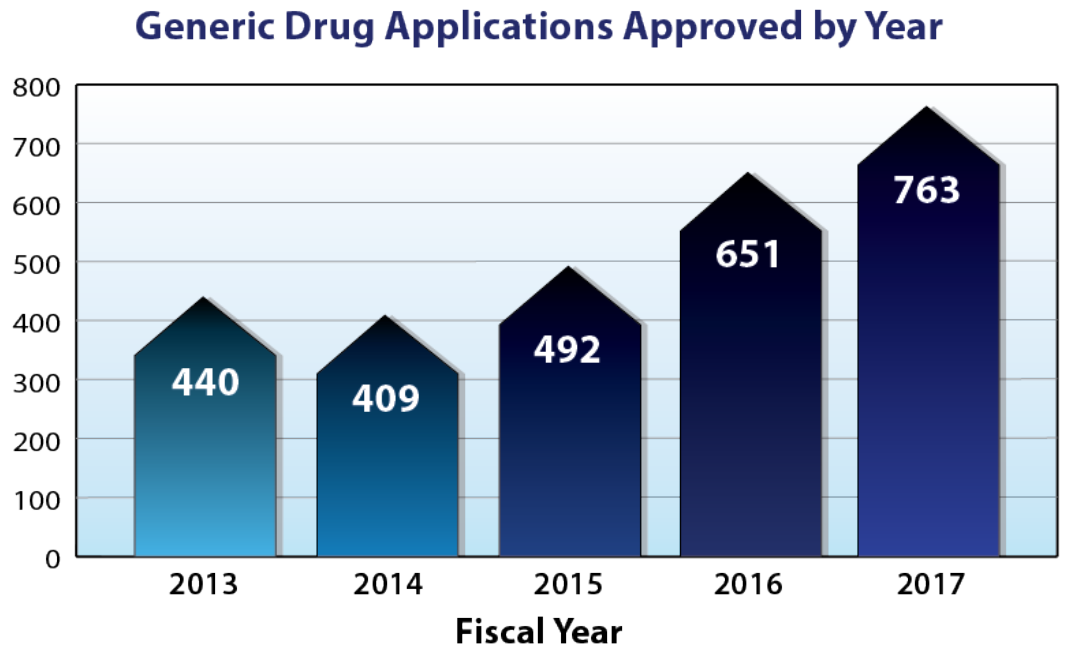
- For products with systemic site of action, BE via systemic PK endpoints (e.g. C_{max} and AUC) helps infer comparable safety and efficacy
- For products that are locally acting, it is more difficult to assess local exposure
- The site of action may not be directly correlated with systemic PK

GDUFA* Pharmaceutical Science

- FDA has a role in advancing drug science and pharmacologic knowledge helps increase drug access by providing science-based methods and standards for determining equivalence.
- ~$25 million per year on stakeholder-driven generic drug regulatory science
  - Goal: Access to generics in all product categories
  - 90+ on-going projects
  - Recent focus on complex products

*GDUFA = Generic Drug User Fee Act

Generic Drug Science & Research Website:
https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm



Complex Generic Products in GDUFA II

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables and implantables, transdermals, MDIs
- Complex drug-device combination products
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

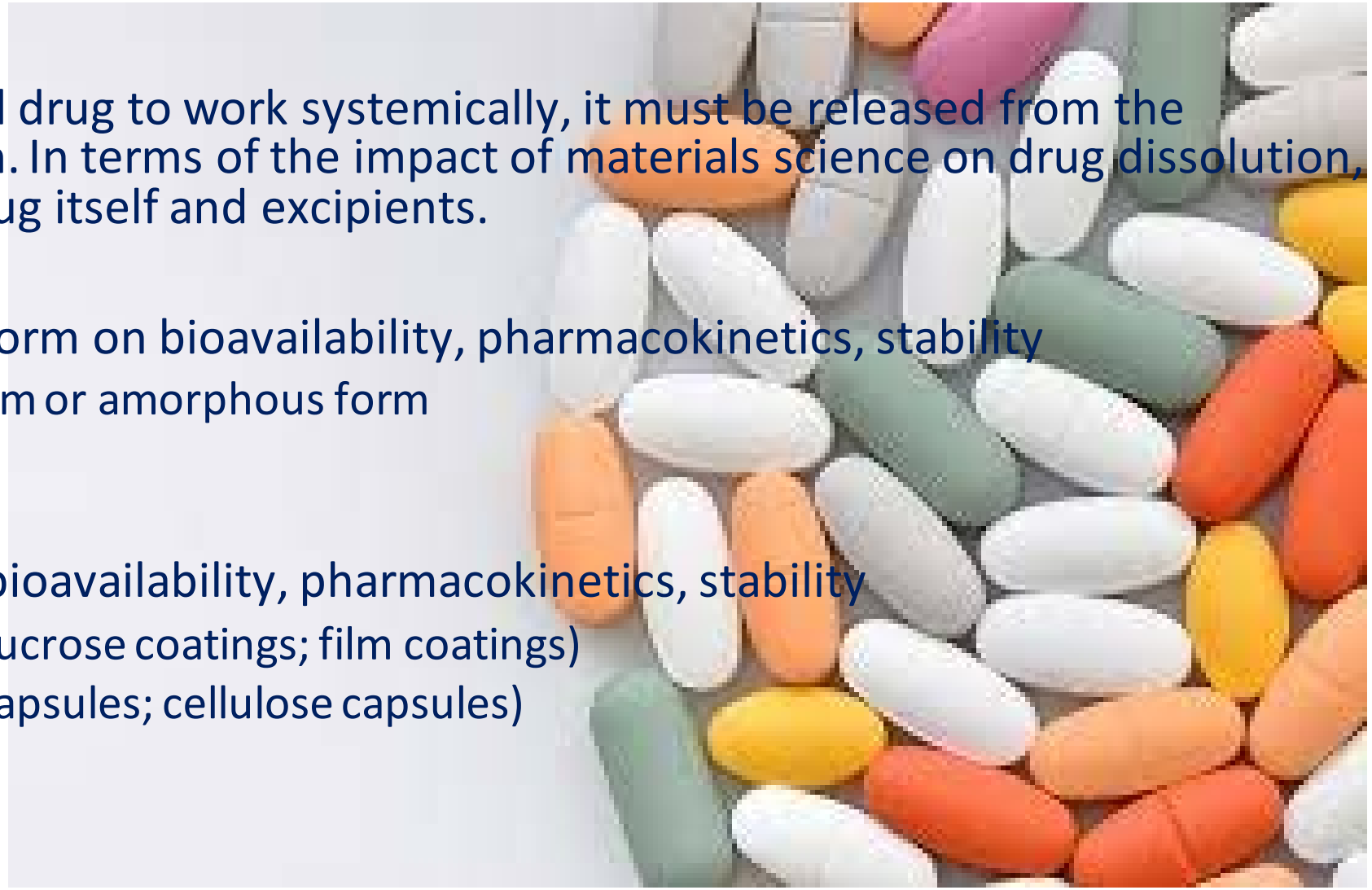
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Drug Product Materials Science

- Complex drug products involve using of various biomaterials. Pharmacologic science of drug delivery continues to evolve and innovate.
- This area ranges from relatively simple orally-administered immediate-release products to modified-release formulations.
- Further, drug delivery via routes other than oral each have their own well-developed technology and may involve unique materials consideration.

Oral Drug Product Materials Science

For an orally-administered drug to work systemically, it must be released from the formulation by dissolution. In terms of the impact of materials science on drug dissolution, it comes from both the drug itself and excipients.



- Effect of drug product form on bioavailability, pharmacokinetics, stability
  - Optimal crystalline form or amorphous form
  - Particle size

- Effect of excipients on bioavailability, pharmacokinetics, stability
  - Tablet Coatings (i.e. sucrose coatings; film coatings)
  - Capsules (i.e. gelatin capsules; cellulose capsules)

Abuse deterrence Formulations and Materials

- Some materials are used in drug formulations to try to thwart abuse of the product.
- These include materials that may result in making pills more difficult to crush into powder.
- Coatings or encapsulations may be used to sequester another drug, e.g. an opioid antagonist that would be released upon crushing, but not released during normal passage thru the GI tract.

Injectable Complex Drug Product Materials Science

Injectable complex drug products are advanced dosage forms which involve using various biomaterials.

Complexity in excipients and formulation design requires in depth research to develop appropriate methodologies for analyzing and characterizing materials and formulations.

Specific examples:

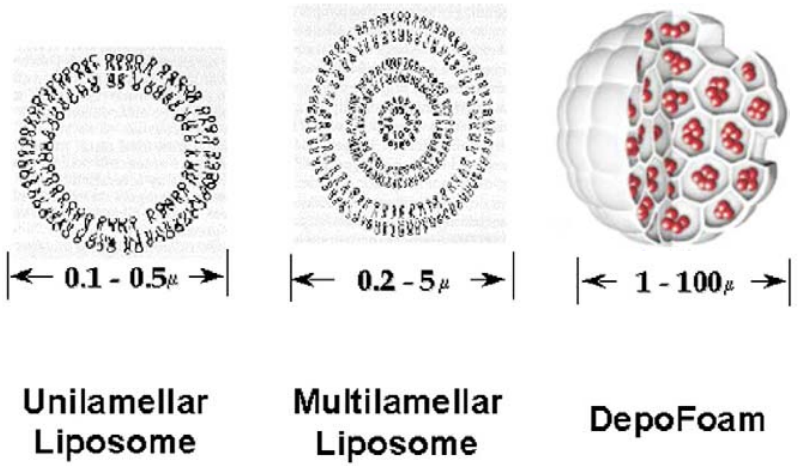
- Multivesicular liposomes
- Polymeric microparticles

FDA Approved Liposomal Products

Trade name	Active Ingredient	Route	Initial Approval Date
Doxil	Doxorubicin HCl	Intravenous	11/17/1995
DaunoXome	Daunorubicin Citrate	Intravenous	4/8/1996
AmBisome	Amphotericin B	Intravenous	08/11/1997
DepoCyt	Cytarabine	Intrathecal	04/01/1999
Visudyne	Verteporfin	Intravenous	04/12/2000
Definity	Perflutren	Intravenous	07/31/2001
DepoDur	Morphine Sulfate	Epidural	05/18/2004
Exparel	Bupivacaine	Intravenous	10/28/2011
Marqibo	Vincristine Sulfate	Intravenous	08/09/2012
Onivyde	Irinotecan HCl	Intravenous	10/22/2015
Vyxeos	Daunorubicin and Cytarabine	Intravenous	08/03/2017

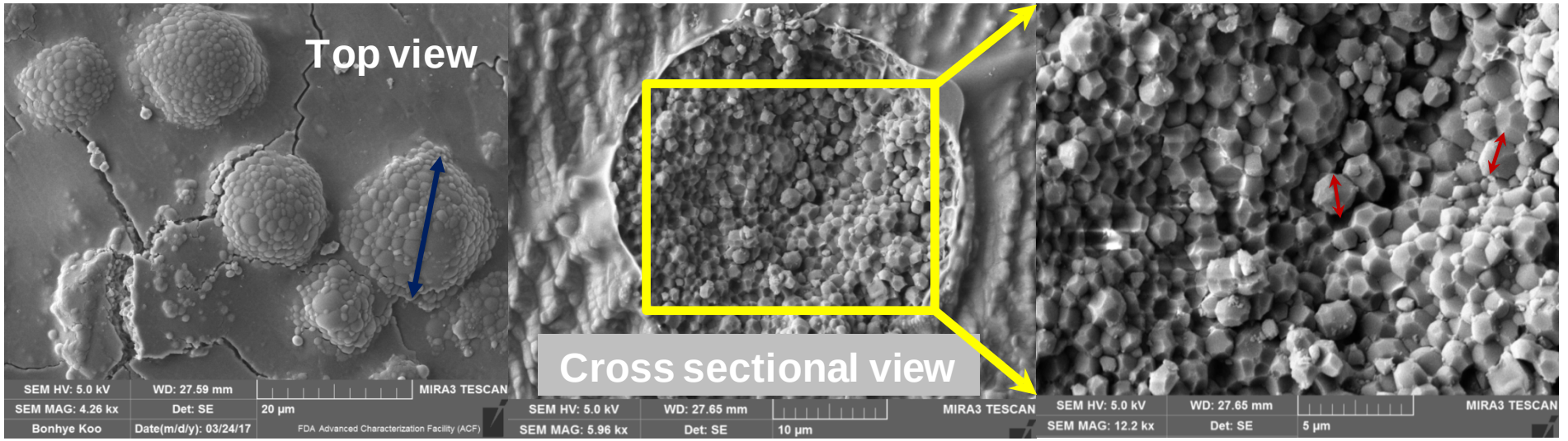
- Multivesicular liposome – DepoFoam® drug delivery system[1]
- DepoFoam® - How is it different ?
  - **Uni**lamellar – **single** lipid bilayer
  - **Multi**lamellar – **multiple concentric** lipid bilayers
  - **Multivesicular**– **multiple non-concentric** lipid bilayers
    - at least one amphiphatic lipid (phospholipids)
    - at least one neutral lipid (triolein, tricaprylin, tributyrin) [2]
    - increased stability
    - prolonged duration of drug release
    - higher entrapment of hydrophilic drugs

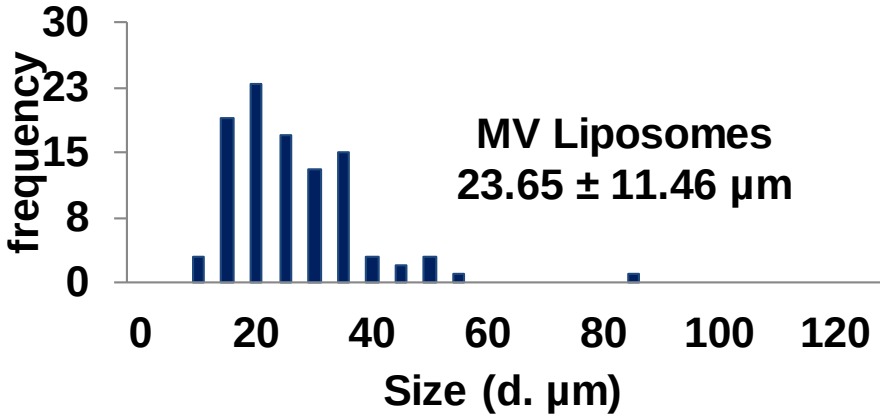
Advantages

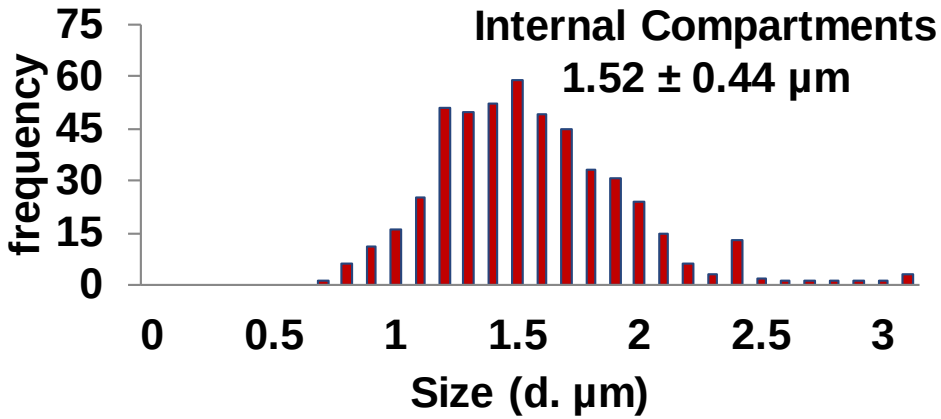


[1]Mantripragada, Progress in Lipid Research; 2002

[2]Jain et al. Drug Delivery; 2007

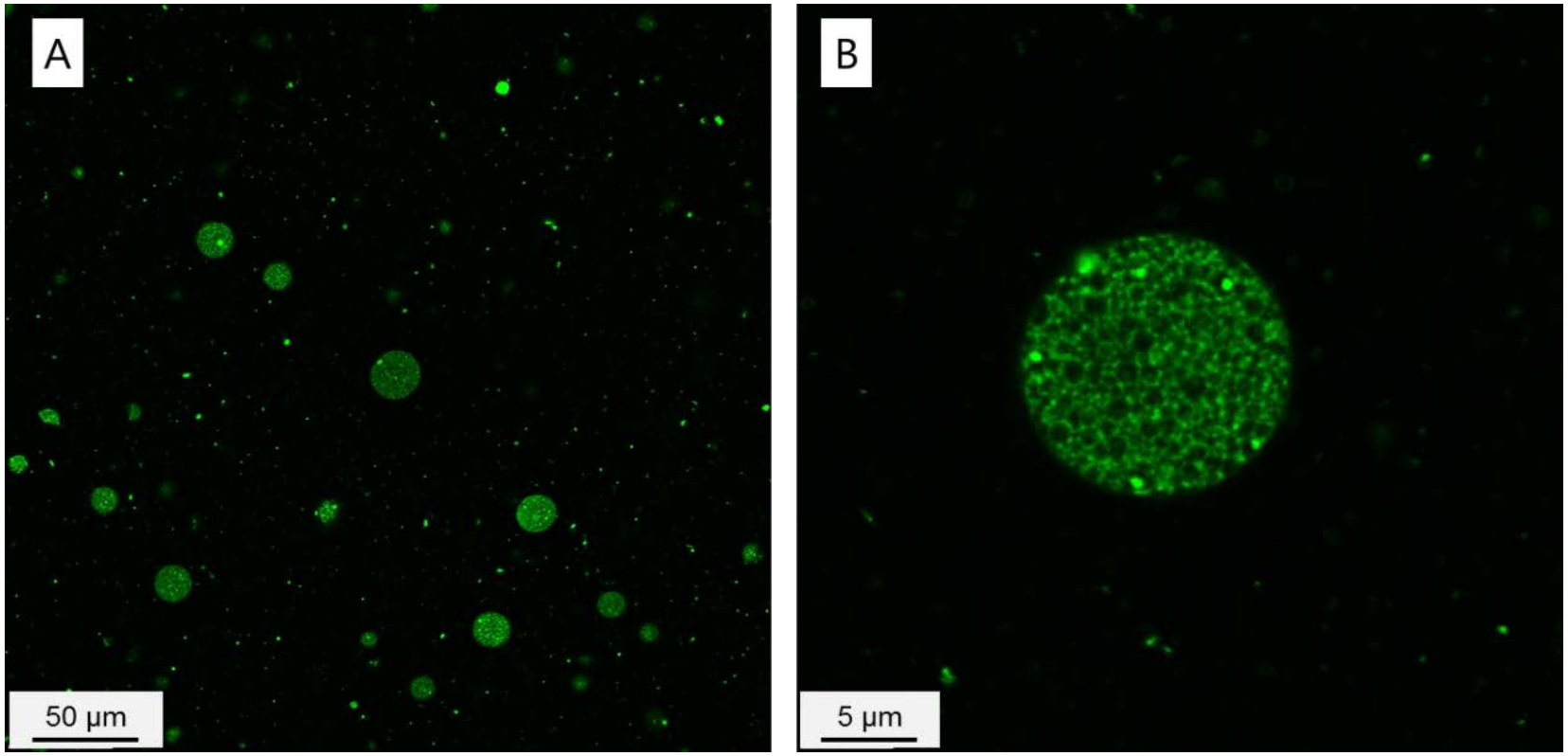






Mostly spherical shape structure; Size range of 10 - 60µm

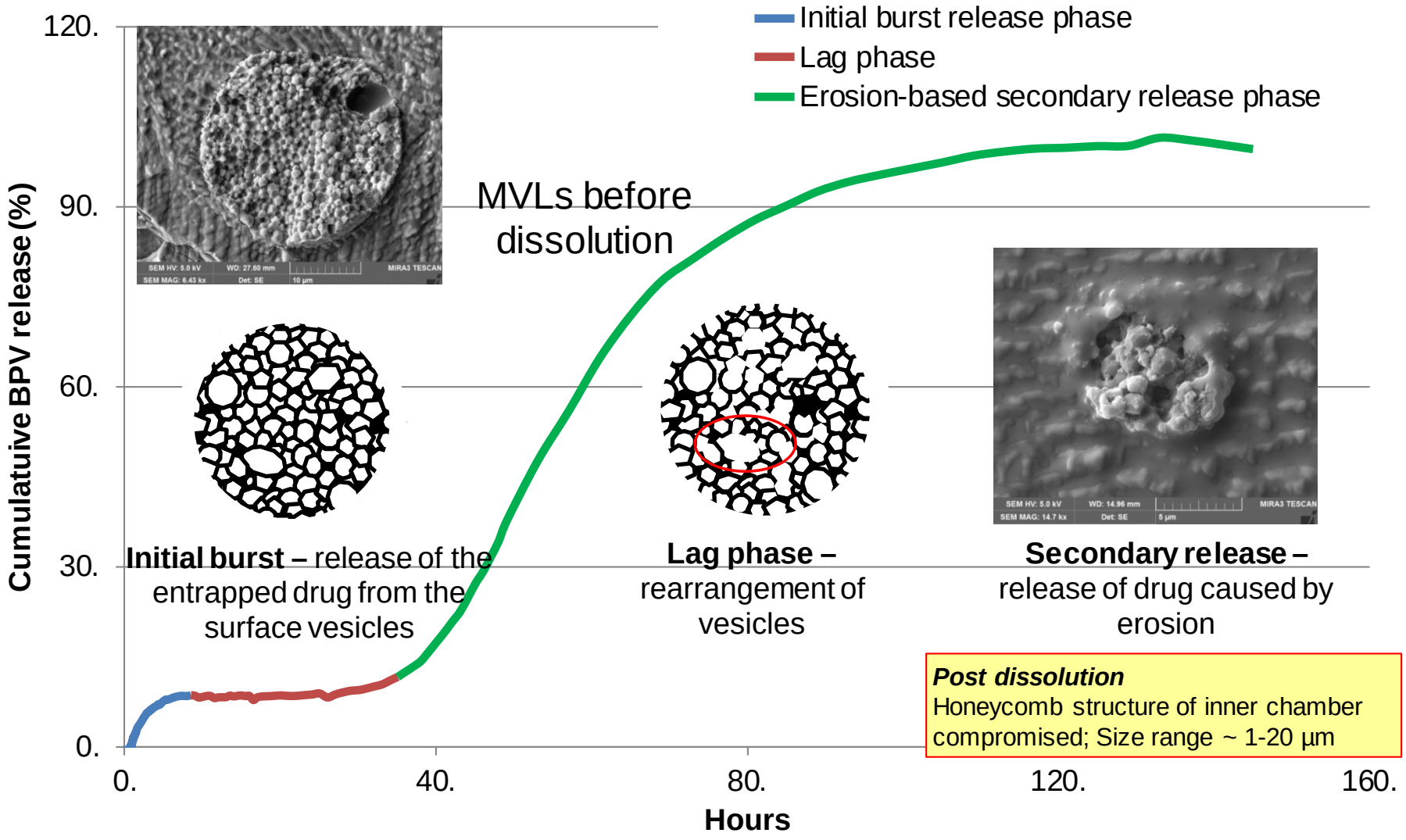
Confocal Microscopy



- **BODIPY™ 500/510** - C4, C9 (5-Butyl-4,4-Difluoro-4-Bora-3a,4a-Diaza-s-Indacene-3-Nonanoic Acid) was used as the f
- Stock samples of BPV-I (DEPC:BODIPY)
- Samples were then **incubated** at room temperature in a **dark room** for **1 hour**
- Prior to confocal imaging, samples were **diluted 10x** in PBS buffer

Internal compartments show the characteristic "honeycomb" structure
Range of 1 - 2 µm - consistent with cryo-SEM results
Can be used as a complimentary method to cryo-SEM

Working Hypothesis – Release Mechanism



Soumyarwit Manna, Ph.D.

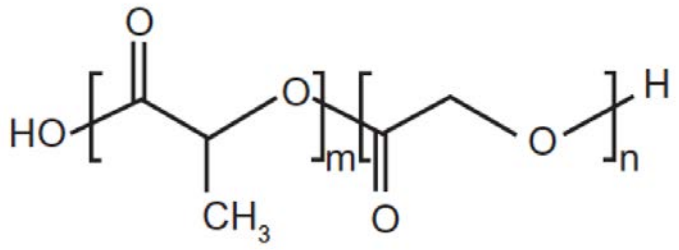
PLA/PLGA-based LAI Drug Products

Drug Product (Active Ingredient)	Dosage Form	Route of Administration	Indication(s)
Ozurdex (Dexamethasone)	Implant	Intravitreal	macular edema, non-infectious uveitis, and diabetic macular edema
Zoladex (Goserelin acetate)	Implant	Subcutaneous	Prostate cancer
Atridox (Doxycycline hyclate)	In situ forming gel	Periodontal	periodontitis
Eligard (Leuprolide acetate)	In situ forming gel	Subcutaneous	advanced prostate cancer
Lupron (Leuprolide acetate)	Microsphere	Intramuscular	endometriosis
Lupron Depot (Leuprolide acetate)	Microsphere	Intramuscular	advanced prostatic cancer
Lupron Depot-PED (Leuprolide acetate)	Microsphere	Intramuscular	central precocious puberty
Trelstar (Triptorelin pamoate)	Microsphere	Intramuscular	advanced prostate cancer
Risperdal Consta (Risperidone)	Microsphere	Intramuscular	schizophrenia and bipolar I disorder
Signifor LAR (Pasireotide pamoate)	Microsphere	Intramuscular	acromegaly
Vivitrol (Naltrexone)	Microsphere	Intramuscular	alcohol dependence
Arestin (Minocycline HCl)	Microsphere	Periodontal	periodontitis
Bydureon (Exenatide)	Microsphere	Subcutaneous	type 2 diabetes
Sandostatin LAR (Octreotide)	Microsphere	Subcutaneous	acromegaly
Signifor (Pasireotide)	Microsphere	Subcutaneous	cushing's disease

PLA=Poly Lactic Acid, PLGA=Poly Lactic-co-Glycolic Acid, LAI=Long Acting Implantable/Injectable

Complex Excipients

- **Poly(lactic-*co*-glycolic acid) (PLGA) copolymer**

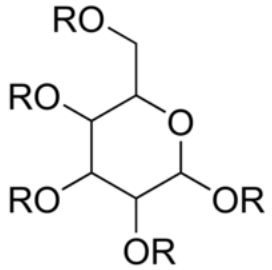


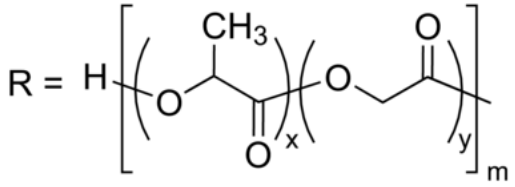
PLGA

m = number of units of lactic acid
n = number of units of glycolic acid

- Ratio of lactic acid to glycolic acid
- Molecular weight/weight distribution

- **Glucose star polymer, D,L-lactic and glycolic acids copolymer**





Sandostatin LAR depot
(octreotide acetate microsphere)

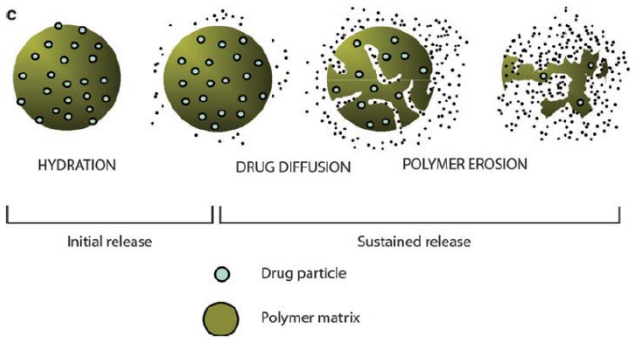
http://www.sigmaaldrich.com/catalog/product/aldrich/764876?lang=en&region=US

Complex Drug Release

- **Multiple factors impact drug release**

  Polymer composition; polymer molecular weight; API chemical property; manufacture process; matrix size and shape; drug loading; pH; releasing media……

- **Complex drug release mechanisms**
  - ➢ Multi-phasic release profiles

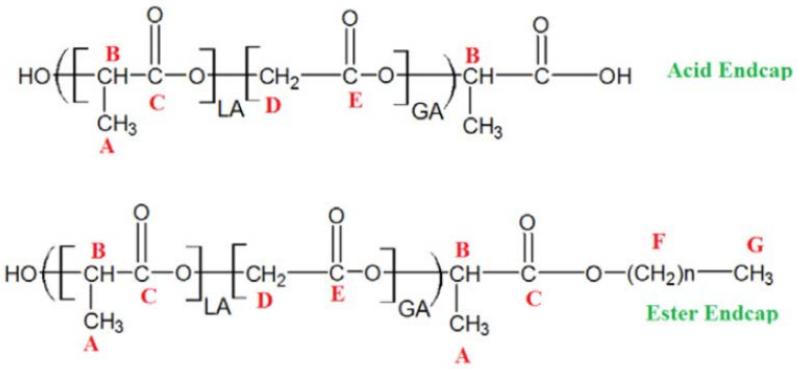


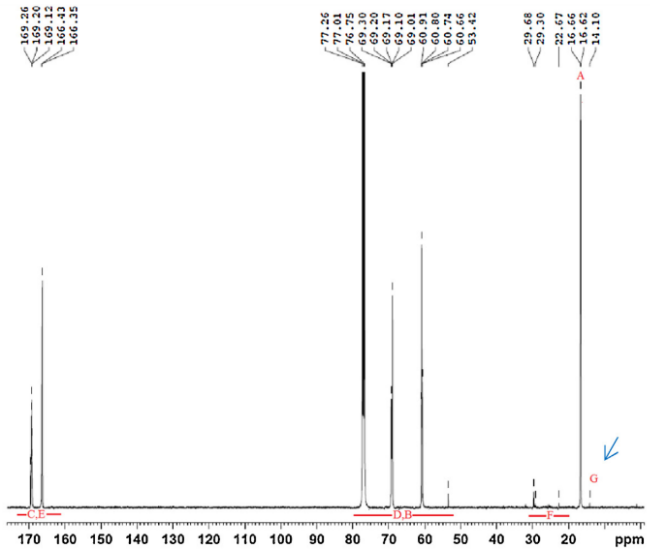
- **No compendial in vitro drug release testing method**
  - ➢ Unlike oral formulations, no standardized test procedures (e.g., USP methods) for parenteral microsphere products.
  - ➢ The process of establishing release method and acceptance criteria is complicated.
- **Challenging to correlate in vitro drug release with in vivo pharmacokinetics**

DeYoung MB et. al. Diabetes Technol Ther. 2011 Nov;13(11):1145-54 http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM399483.pdf

Characterizations of PLGAs

- Development of advanced analytical techniques





From product-specific guidance of risperidone injection

The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference product for all strengths (12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial). Please provide characterization data on poly(lactide-co-glycolide) (PLGA) for both the test and reference product including polymer composition (ratio between glycolic acid and lactic acid), molecular weight and weight distribution, and PLGA architecture (e.g., linear or star-branched PLGA). Additional data on PLGA characterization may be requested during the review of the ANDA.

Garner J, et al. Int J Pharm. 2015 Aug 28;495:87-92

Complex Drug Product:
Drug-Device Combination Products

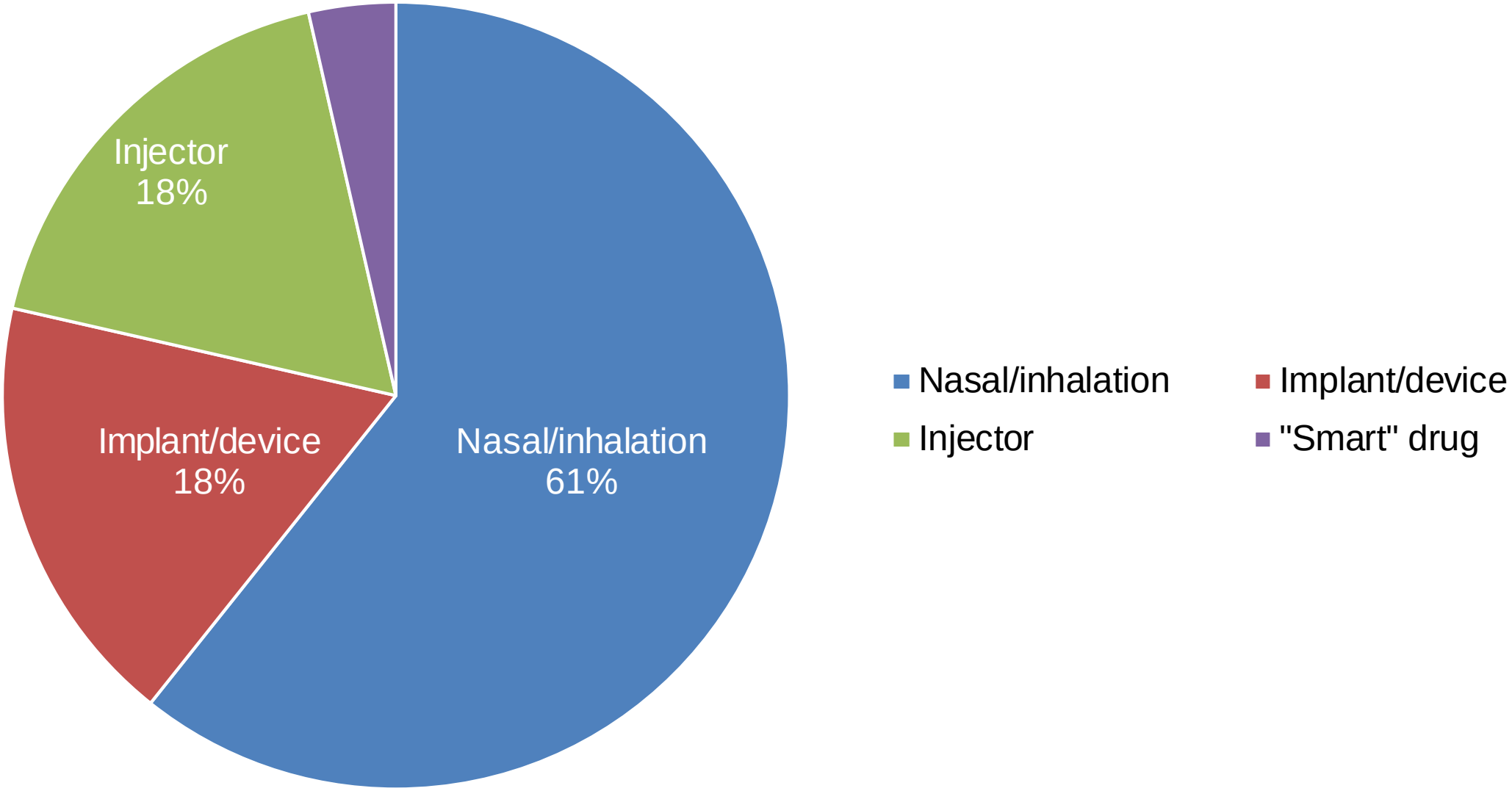
Drug Products with Device Components

- There are some drug products that are regulated in CDER by the FDA that have a primary mode of action that is associated with the drug.
- These products are known as Drug-Device Combination Products.
- These products are approved under new drug provisions and are eligible for generic drug competition.

What kinds of drugs are combination products and eligible for generic competition?

- Solutions in autoinjectors
- Inhaled drug products
- Topical transdermal drugs for systemic delivery
- Drugs that are injected or implanted and then released slowly
- Drugs that are activated through exposure to light energy to form a cytotoxic substance to treat certain tumors

Complex NDA Drug Products with Device Components 2015-2017 (N=28)



Drug-Device Combination Products

- What are some functions of the medical device component of a Drug-Device Combination Product?
  - to provide a mechanism to deliver the drug to the patient
  - to regulate the rate of drug release to the patient, e.g. modified release/delayed release by mechanical means
  - to monitor the delivery of drug
  - to modify the drug substance by delivering energy to affect a chemical reaction

Intrauterine Systems – GDUFA research

Intrauterine Devices and Intrauterine Systems in the U.S.

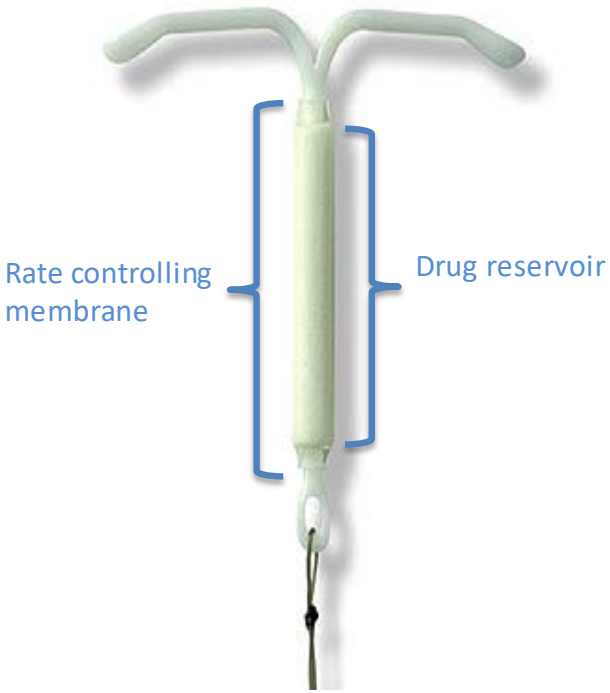
- Copper intrauterine devices (IUDs)
  - Paragard T 380A: up to 10-year use, Teva Women Health

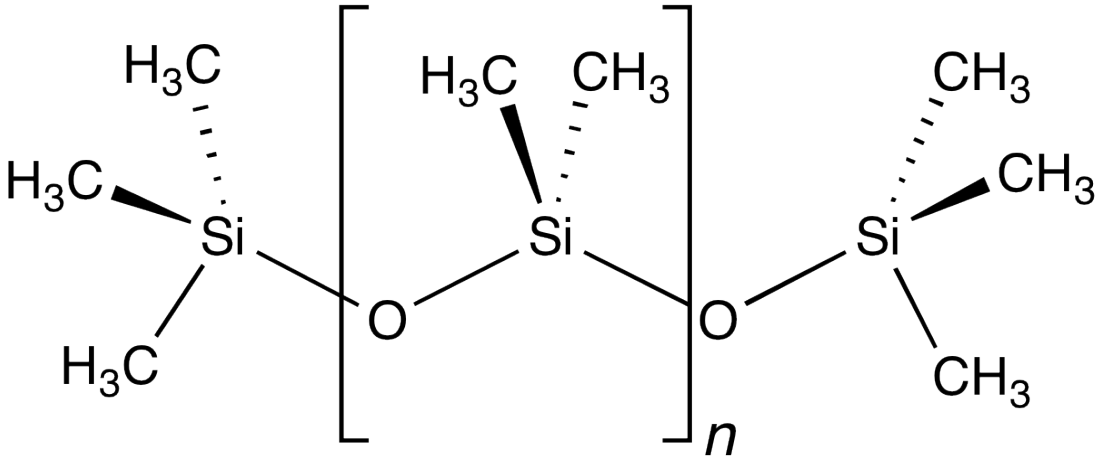
- Levonorgestrel-releasing intrauterine systems (IUSs)
  - Mirena: 52 mg, up to 5 years use, Bayer HealthCare
  - Slyla: 13.5 mg, up to 3 years use, Bayer HealthCare
  - Kyleena: 19.5 mg, up to 5 years use, Bayer HealthCare
  - Liletta: 52 mg, up to 4 years use, Medicines360

Advantages

- Effective, safe, and reversible contraception
- Less user dependent
- More cost-effective than oral contraception even at 1 year of use

Drug Releasing Intrauterine Device – From Labeling





PDMS – A group of silicon based organic polymers.

Drug released is hormonal contraceptive, e.g. levonorgesterol.

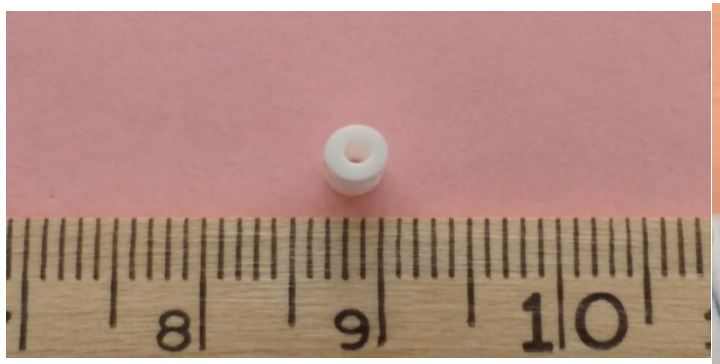
Example of FDA research: FY 2015 RFA

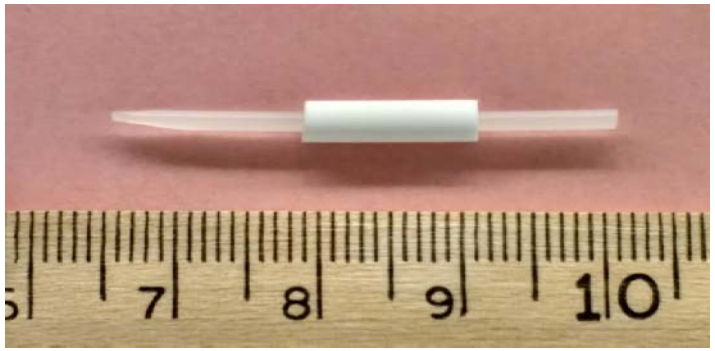
Dissolution methods for long-acting LNG IUS

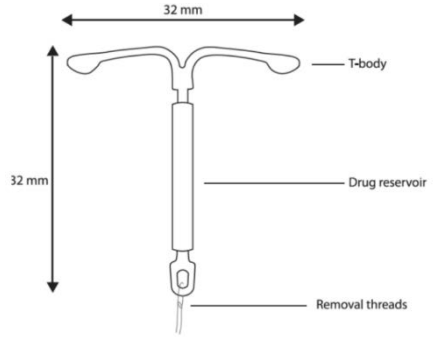
"The objective of this study is to investigate dissolution methods, both real time and accelerated conditions, for levonorgestrel intrauterine systems - LNG IUS (5-year application) and to analyze their capability of detecting manufacturing differences, predicting in vivo performance, and to evaluate method robustness."

RFA = Request For Application

Images of the Prepared IUSs



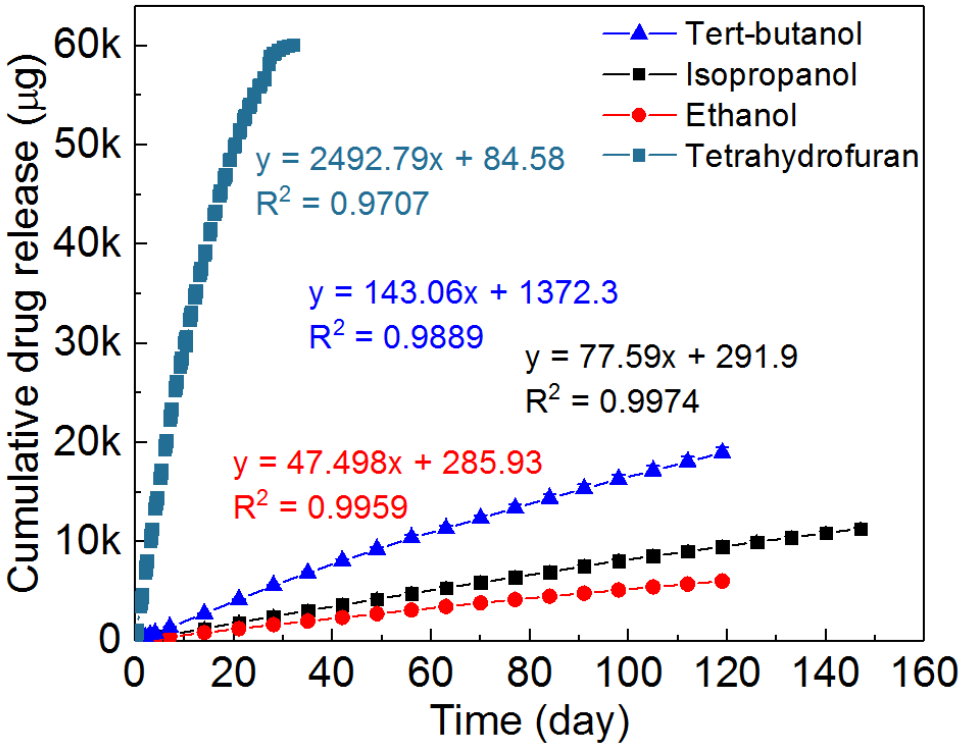




Yan Wang, PhD

Accelerated Release of IUSs in Different Organic Solvents

Release Medium : 20% **Ethanol (EtOH), Isopropanol (IPA), Tert-Butanol (TBA)** and **Tetrahydrofuran** (THF) in pH7.4 PBS with 0.25% SDS
Temperature: 45°C
Incubation: water shaker bath, 100 rpm

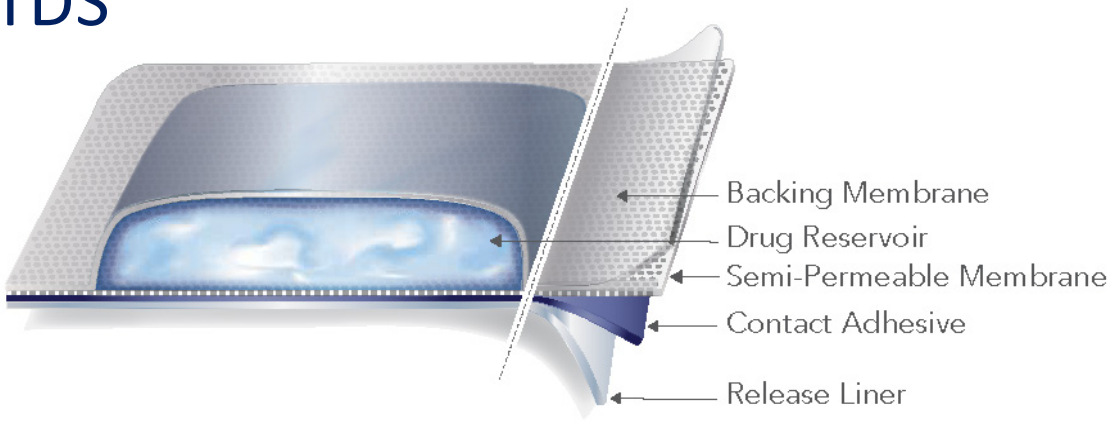


Solvents	Release rate (mcg/d)	ratio
EtOH	47.50	1
IPA	77.59	1.63
TBA	143.06	3.01
THF	2492.79	52.48

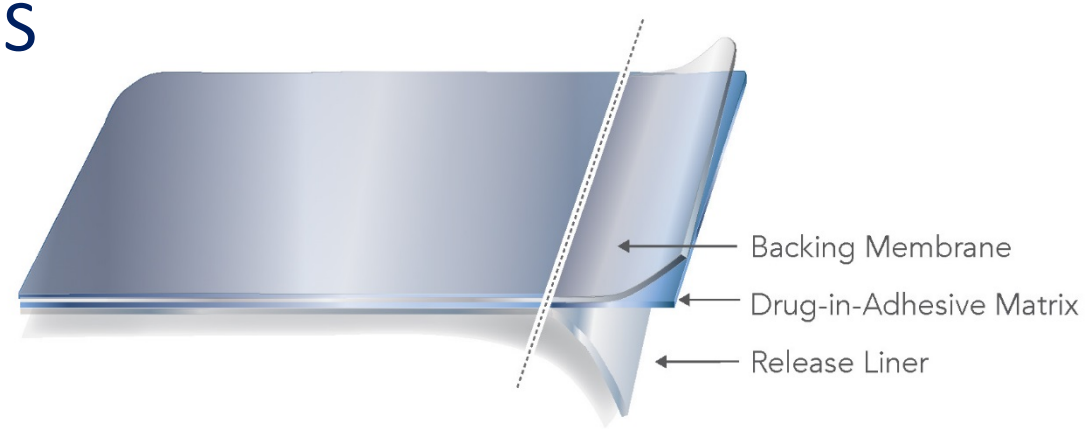
Yan Wang, PhD

Transdermal Systems (TDS)

- **Dosage Form**
  - Reservoir TDS

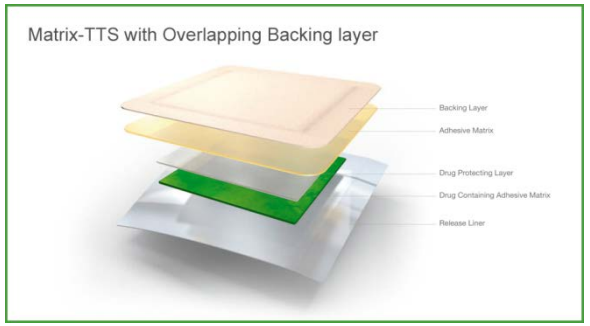


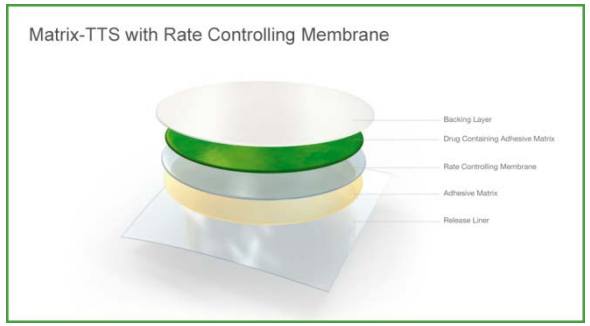
  - Matrix TDS

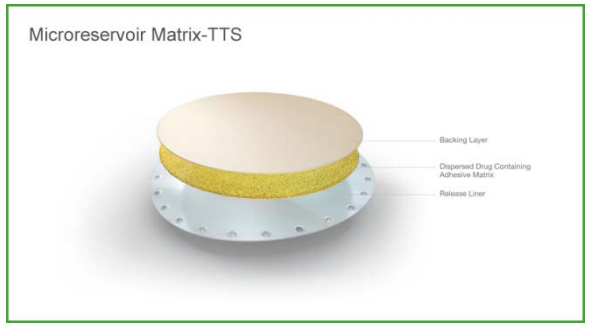


Special Considerations for Generic TDS

- **Dosage Form**
  - Design variation even among “Matrix” TDS





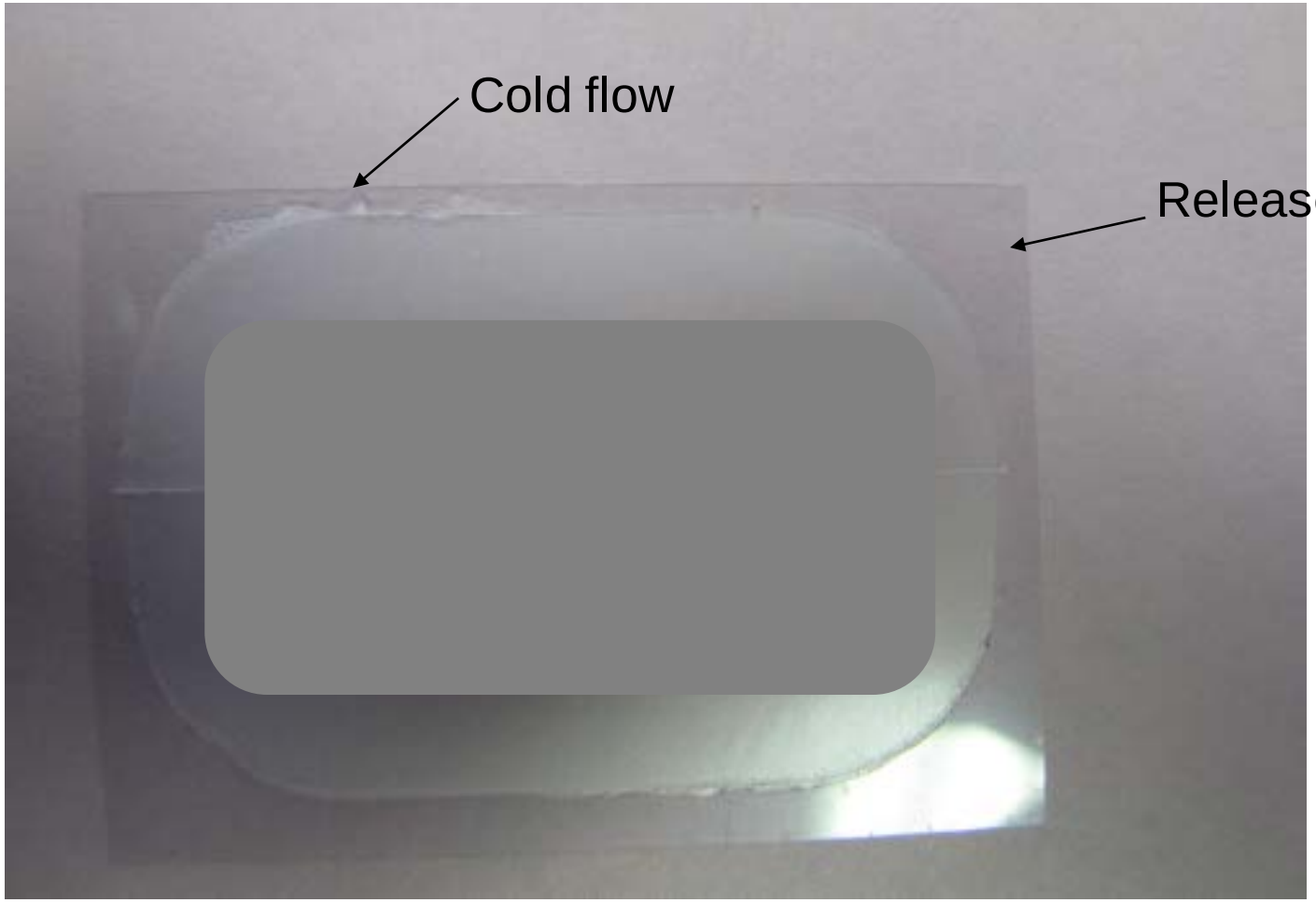


IMAGE(S) SOURCE: All from https://ltslohmann.de/en/technology/transdermal-therapeutic-systems/ (last visited 15 NOV 2017)

Stability Issue: Cold Flow

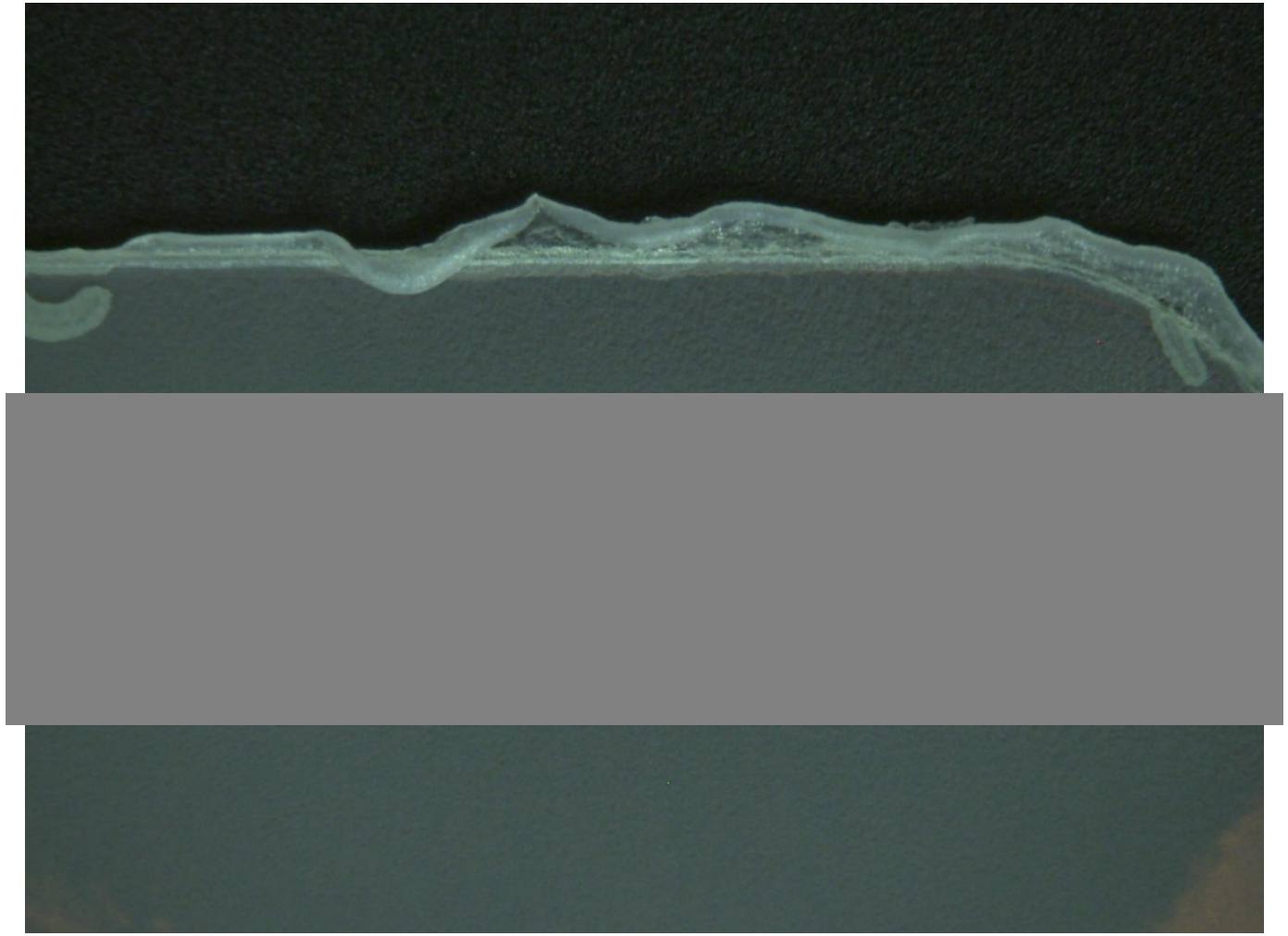
- Cold flow: Movement of adhesive beyond the edge of a TDS
- Patient-use issues
  - Difficulty removing from pouch
  - Sticking to clothing/detachment from skin
- Safety
  - Unintentional exposure
  - Higher drug delivery (increased effective surface area)

Stability Issue: Cold Flow



Pictures compliments of Anna Wokovich, CDER, St. Louis, MO

Stability Issue: Cold Flow



Pictures compliments of Anna Wokovich, CDER, St. Louis, MO

Stability Issue: Migration

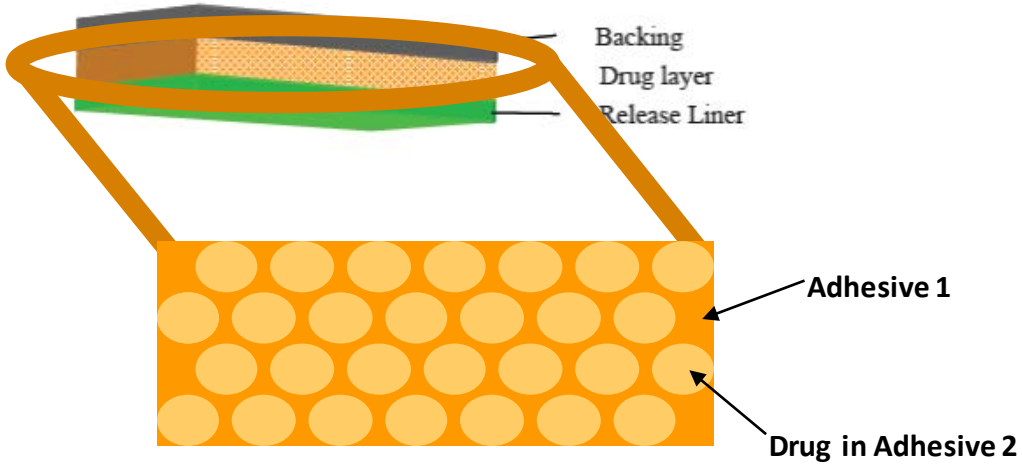
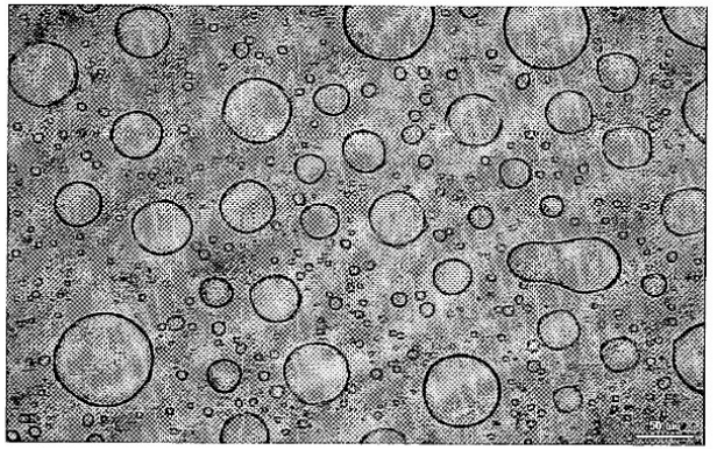
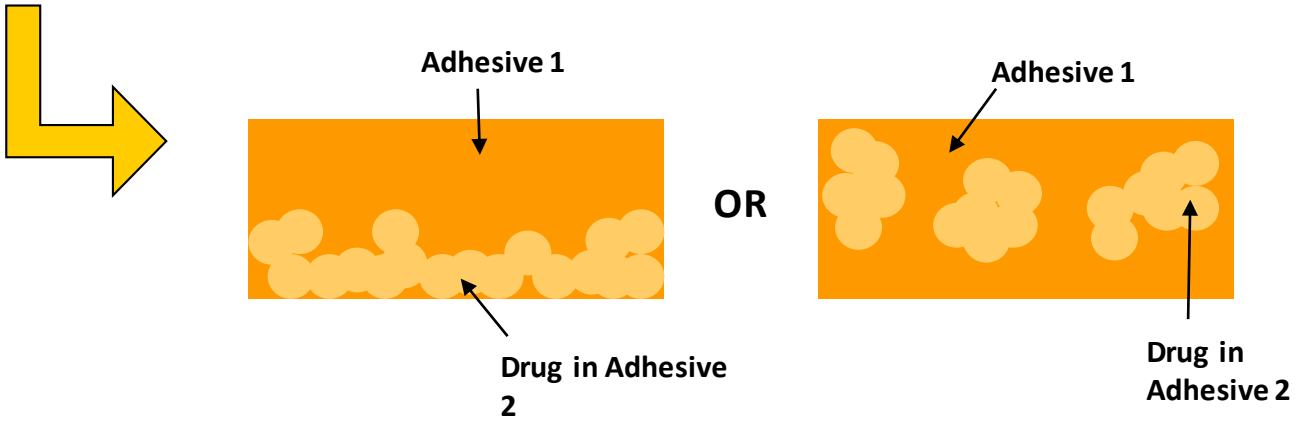


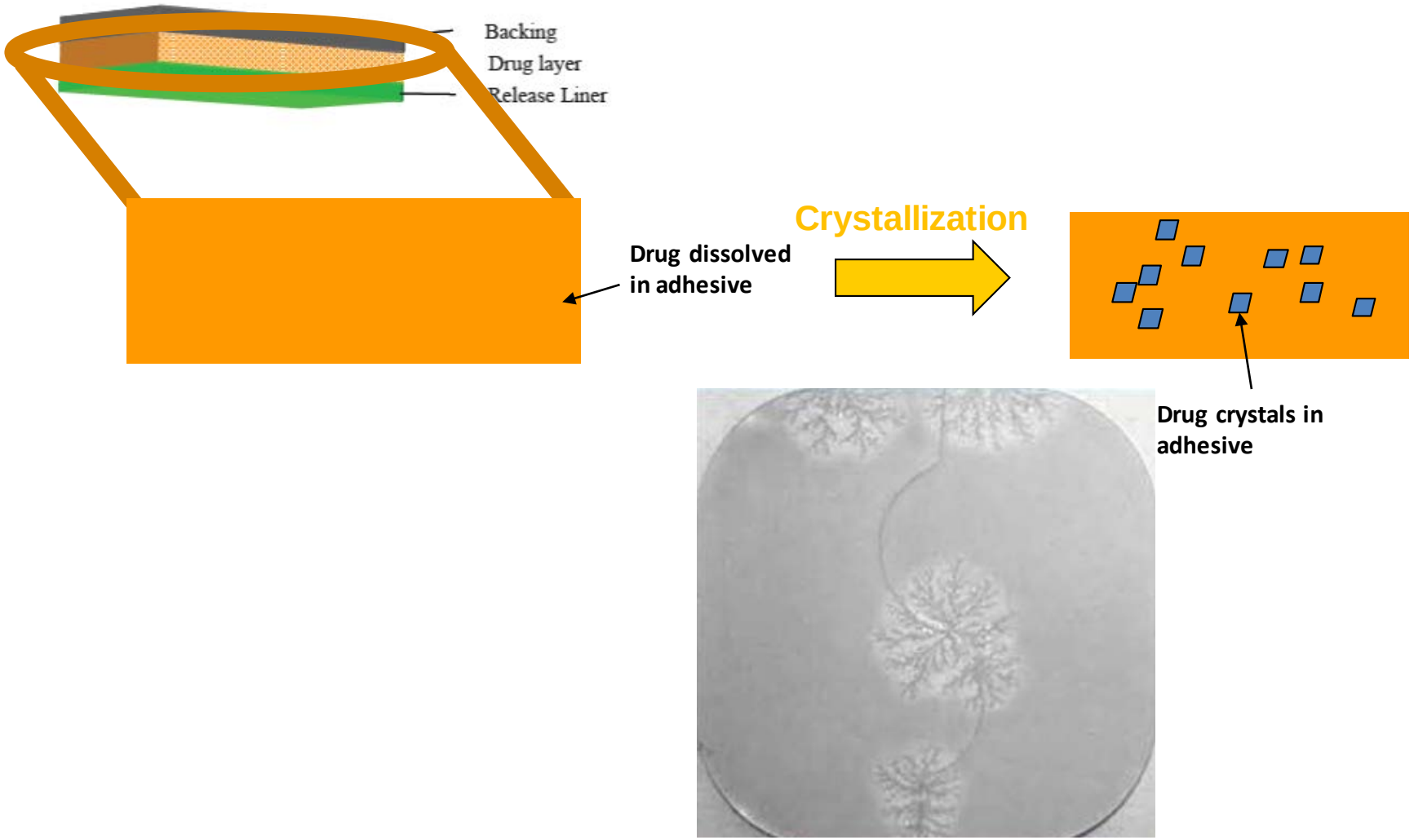
Fig. 4



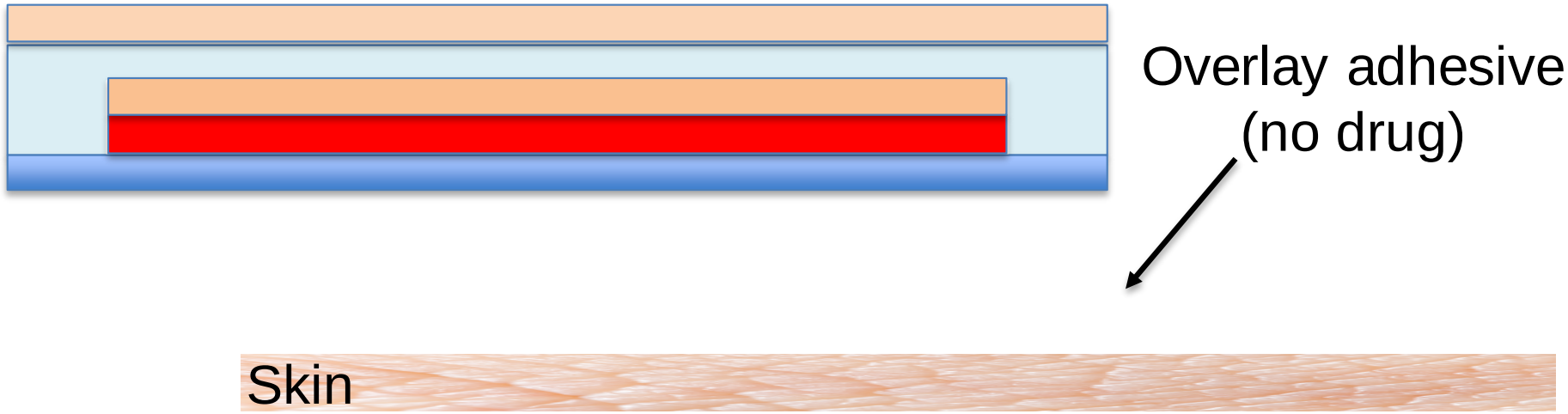
"Transdermal delivery system for the administration of rotigotine"
https://www.google.com/patents/US8246979



Stability Issue: Crystallization

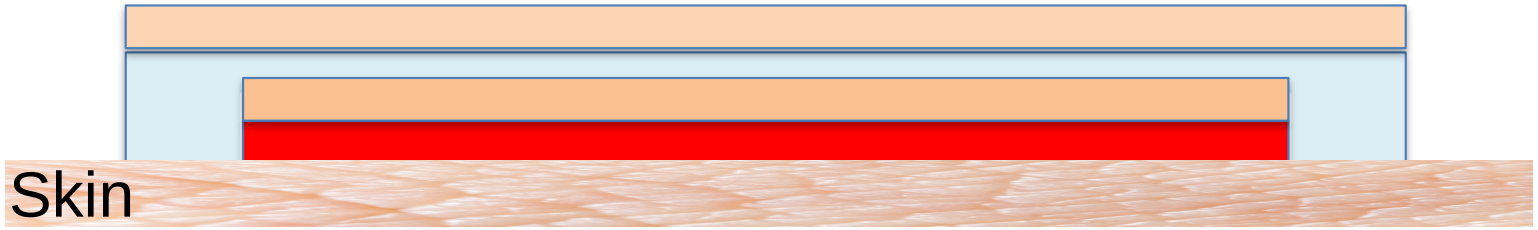


Potential for separation of the overlay adhesive upon removal from packaging



No drug delivery to patient!

Potential for separation of drug from overlay when removing from the skin

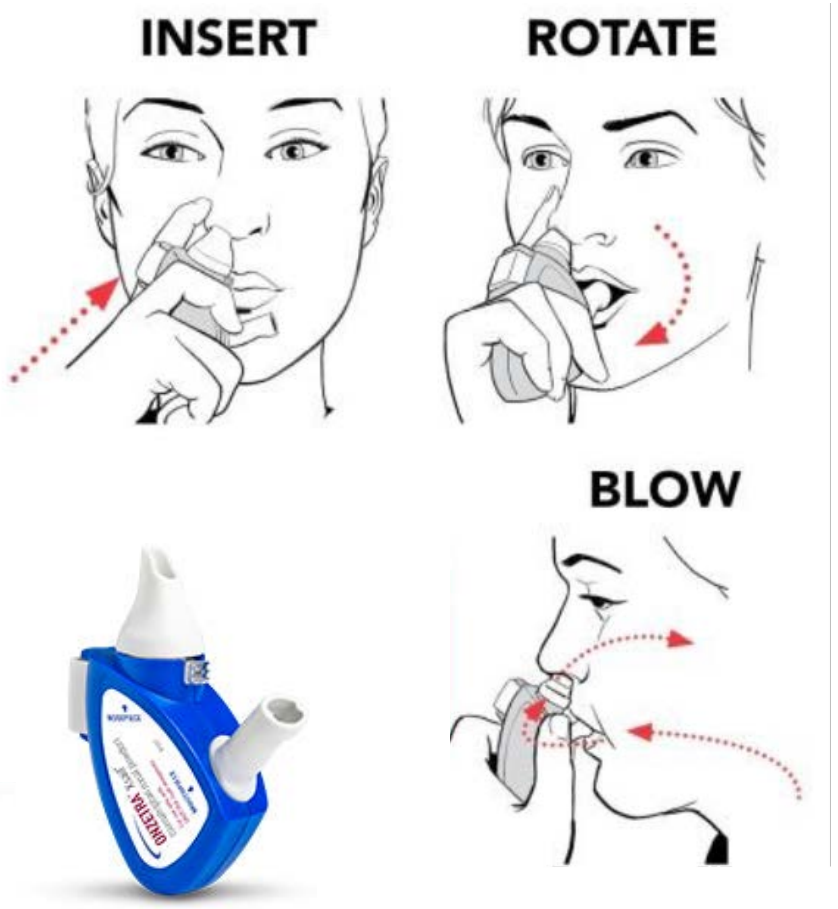


- If active part of the TDS remains on the skin
  - Drug would continue to be delivered
  - Patient may administer an additional TDS, leading to potential super-therapeutic dose

Recently Approved New Drug Products

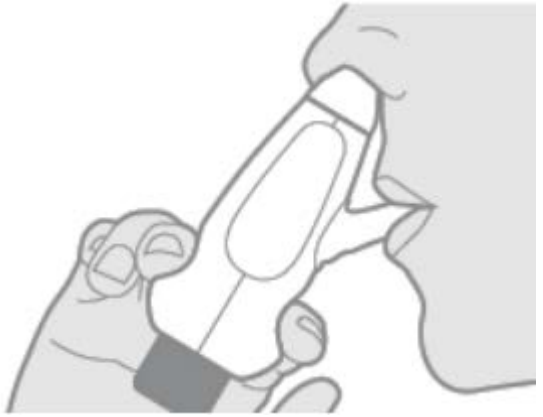
ONZETRA XSAIL

- New approach for the acute treatment of migraine
- Approved: 01/27/2016 (NDA 206099)
- API: Sumatriptan nasal powder
- Dosage Form/Route: nasal powder
- **Complexity**: ONZETRA Xsail is supplied as a disposable nosepiece containing a capsule and a reusable delivery device body. The patient blows forcefully through the mouthpiece to deliver the sumatriptan powder into the nasal cavity.



XHANCE

- New approach to nasal spray
- Approved: 09/18/2017 (NDA 209022)
- API: Fluticasone propionate
- Dosage Form/Route: nasal spray
- **Complexity**: XHANCE is delivered into the nose by actuating the pump spray into one nostril while simultaneously blowing (exhaling) into the mouthpiece of the device.

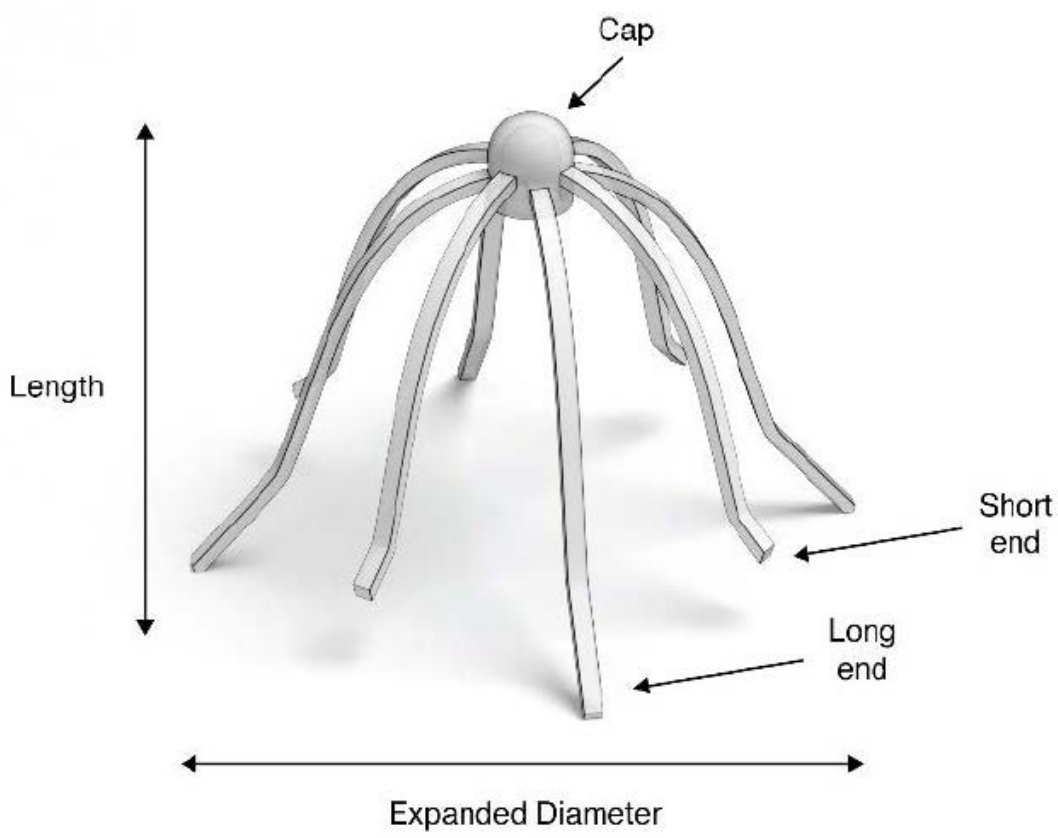


STIOLTO RESPIMAT

- New approach to inhalation spray
- Approved: 05/21/2015 (NDA 206756)
- API: Tiotropium bromide and olodaterol
- Dosage Form/Route: inhalation spray
- **Complexity**: Respimat is a new inhalation drug delivery device and commonly referred to as "Soft Mist Inhaler"

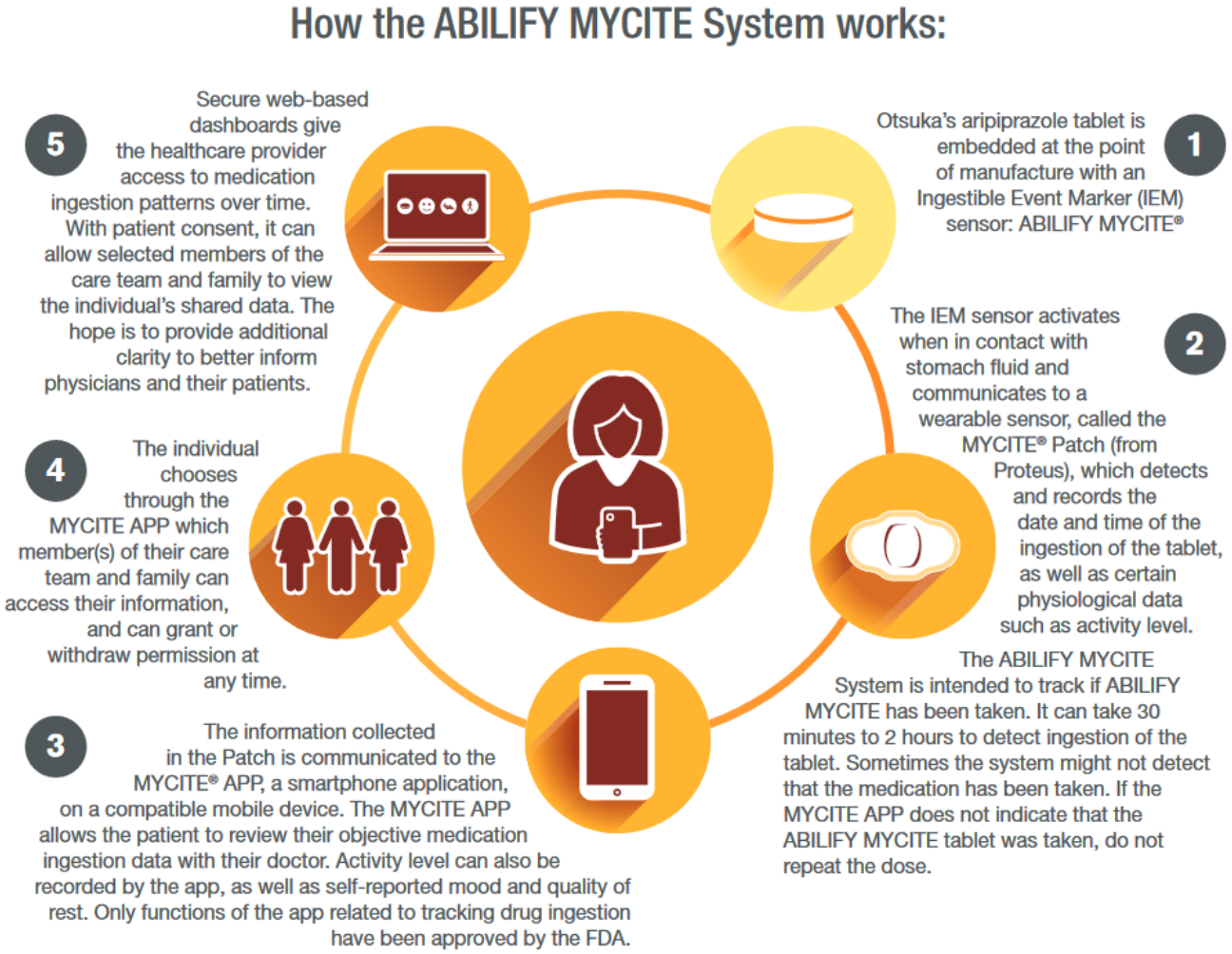
SINUVA

- New Approach to Treating Nasal Polyp Disease
- Approved: 12/08/2017 (NDA 209310)
- API: Mometasone furoate
- Dosage Form/Route: Implant; implantation
- **Sinus Implant**: corticosteroid-eluting implant indicated for the treatment of nasal polyps in patients ≥ 18 years of age who have had ethmoid sinus surgery
- **Complexity**: Complex dosage form (i.e., extended release implant); drug-device combination



Smart Pill ABILIFY MYCITE

- First digital ingestion tracking system approved (NDA 207202) in the U.S.
- Approved: 11/13/2017
- API: ARIPIPRAZOLE
- Dosage Form/Route: TABLET;ORAL
- **Indication:** Treatment of adults with schizophrenia; bipolar I disorder; major depressive disorder
- **Complexity:** Drug-device combination



Conclusions

- Certain drug products lend themselves to important material science considerations
- These products often fall in the more “complex” part of the drug product spectrum and as a result may have additional considerations for pharmaceutical and bioequivalence assessments (i.e. for generic drug product development)

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