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Challenges and Development of Transdermal Patches in Perspective Dissolution Studies

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- ***TDDS***
- ***Dissolution Test (General Method)***
- ***Drug Release study of Transdermal Patches***
- ***Challenges and Development***
- ***TDDS is Combination Product?***

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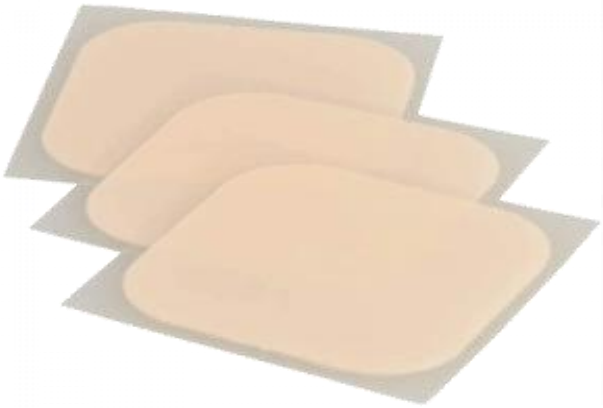
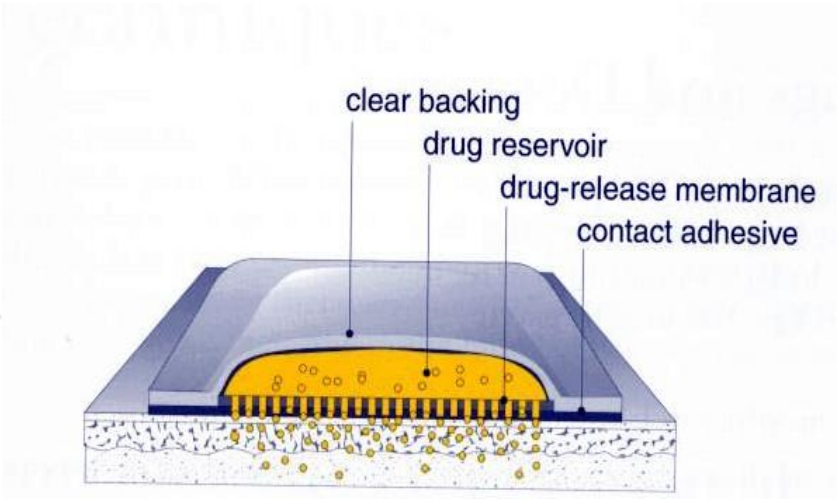
Transdermal Drug Delivery System (TDDS)

- TDDS intends for the treatment or Prevention of Systemic diseases
- TDDS consists of medicated adhesive patches of different sizes, shapes and strengths with one or more active pharmaceutical ingredients (APIs).
- It absorbed through skin in to Blood circulation and transported to target tissues to achieve therapeutic effect





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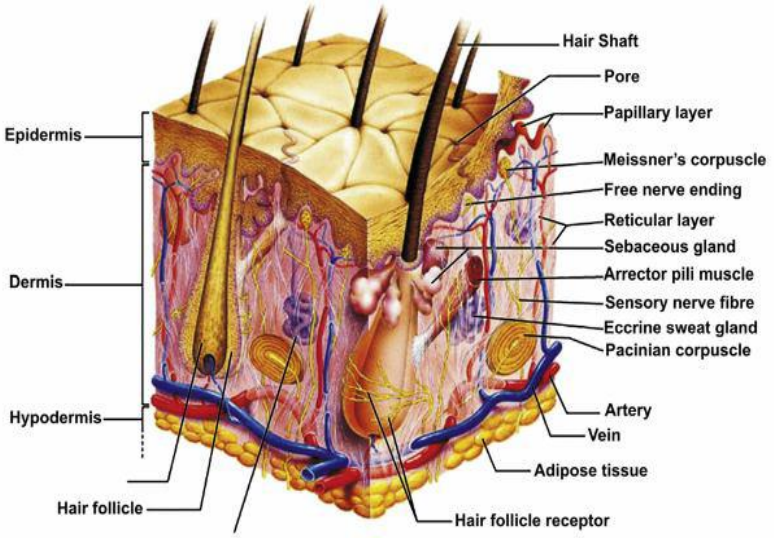
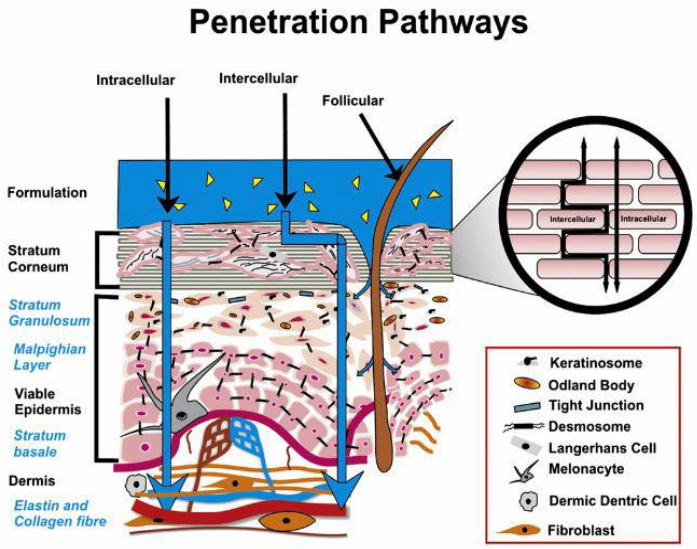
Transdermal Drug Delivery System (TDDS)

- Drug can penetrate through skin via three pathways- **intercellular,**
- **intracellular pathway**,
- and **via hair follicles**, sebaceous glands and sweat duct.





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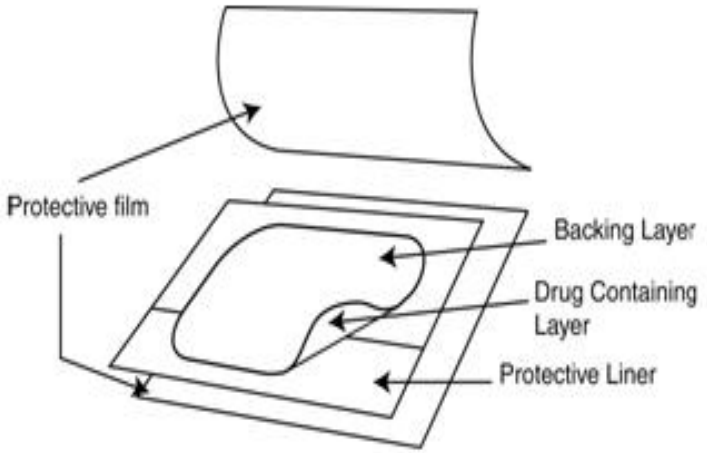
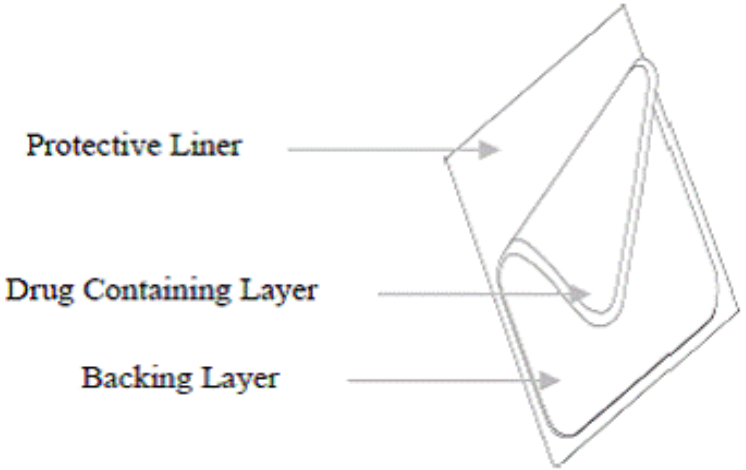
Transdermal Drug Delivery System (TDDS) (Passive diffusion)

- Ideal drug for transdermal drug delivery
- **Dose:** Limited (generally <20mg/day)
- Shorter Half-life Drug
- **Molecular weight:** < 500-400 Daltons.
- The drug should be non-irritating and non-sensitizing for skin
- Drug with low oral bioavailability
- Drug with low therapeutic index





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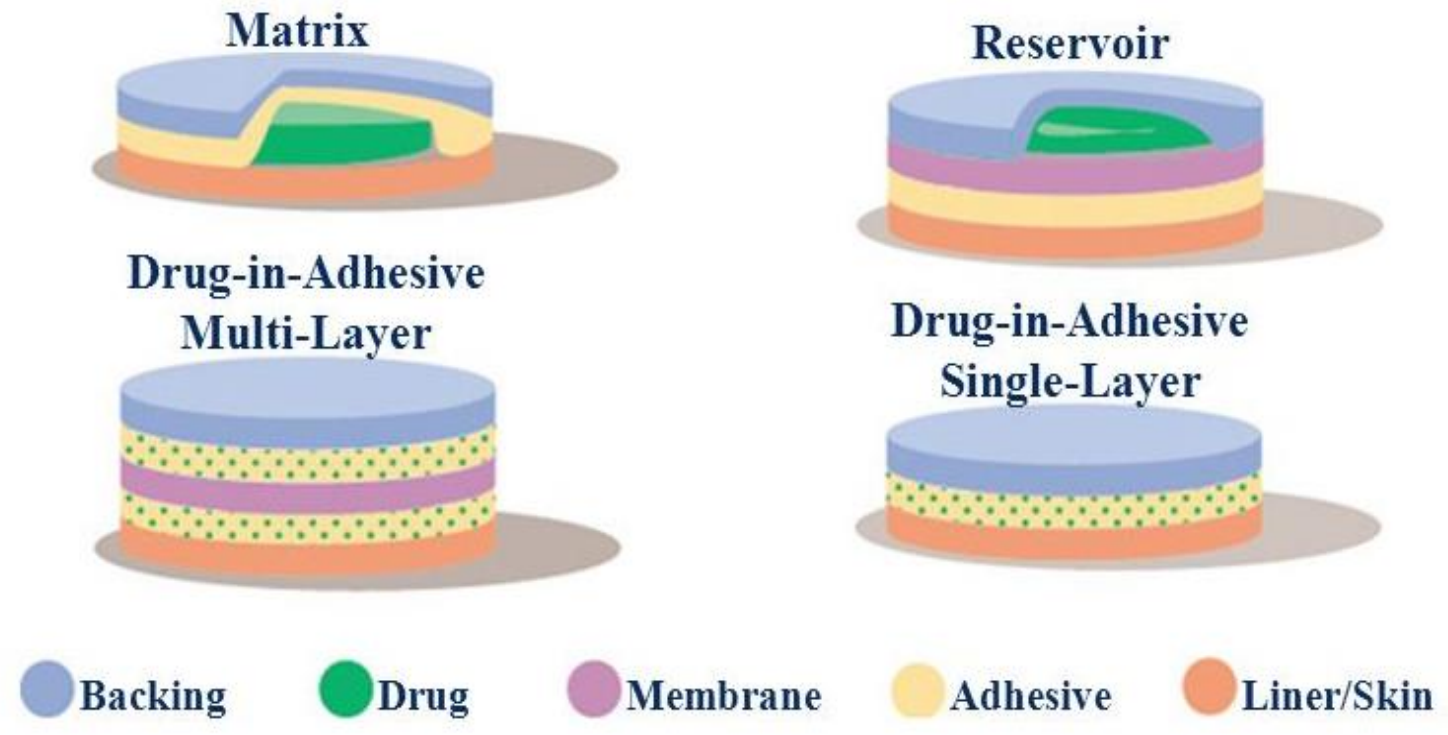
Transdermal Drug Delivery System
- Components and Types -



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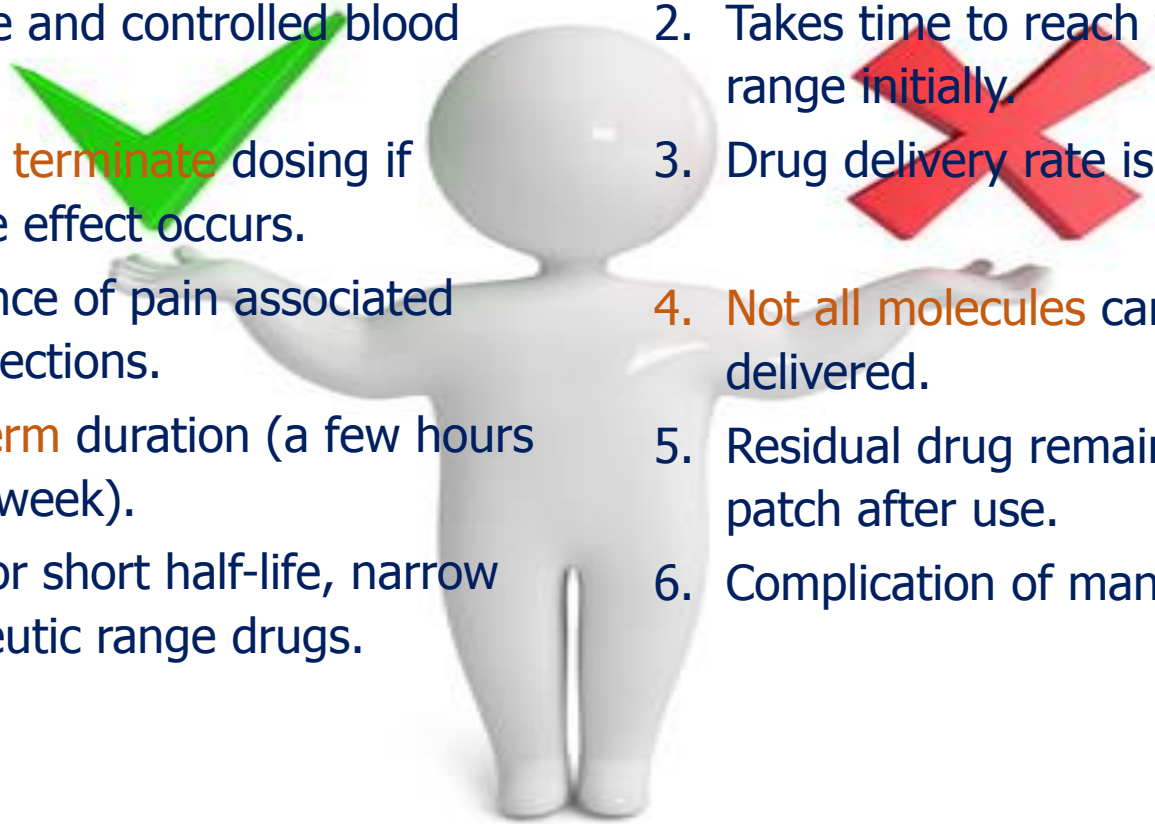
• Advantages

1. Avoidance of the hepatic first pass effect.
2. A stable and controlled blood level.
3. Easy to terminate dosing if adverse effect occurs.
4. Avoidance of pain associated with injections.
5. Long term duration (a few hours to one week).
6. Good for short half-life, narrow therapeutic range drugs.



• Disadvantages

1. Skin irritation/itching sensation may occur.
2. Takes time to reach therapeutic range initially.
3. Drug delivery rate is limited.
4. Not all molecules can be delivered.
5. Residual drug remains in the patch after use.
6. Complication of manufacturing.

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Advantage of Patch

- Patch
  - Controllable drug delivery
    - Fixed dosage area
    - Fixed dosage amount
    - Easy to remove
  - Less Secondary Exposure
    - Release liner
    - Used patch
- Ointment, Cream and Gel
  - Un-Controllable drug delivery
    - Variable dosage area
    - Variable dosage amount
    - Difficulty to remove
  - Much Secondary Exposure
    - Care giver
    - Finger
    - Cloth

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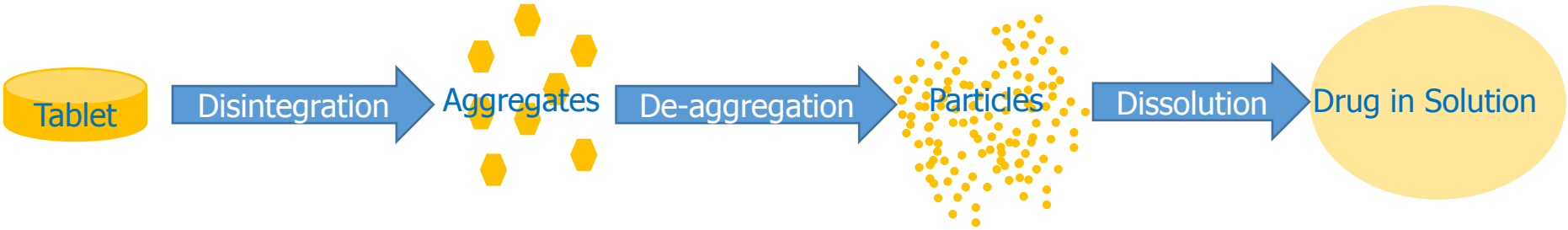
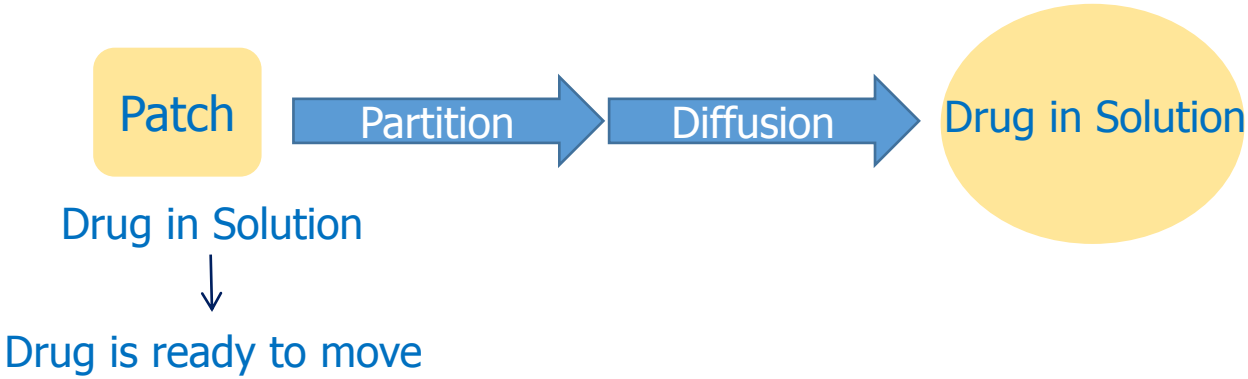
Absorption mechanism



Donald Chaisson, Dissolution Performance Testing of Transdermal Systems, dx.doi.org/10.14227/DT020195P7



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- Evaluation of transdermal patches -

Physicochemical evaluation

- Peel Adhesion, Liner Removal, Shear test, Probe tack and Loop tack test
- Thickness & Uniformity of weight
- Drug Content & Assay
- Impurities
- Residual Solvent
- Pouch Integrity

In vitro evaluation

- **Drug Release (Dissolution Test)**
- Skin Permeation (Diffusion Test)

In vivo evaluation

- Pharmacokinetic and Pharmacodynamic study
- Primary Skin Irritation and sensitization Study
- Adhesion and Photosensitivity Study

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Dissolution Test

- An Overview of In Vitro Dissolution
- Dissolution is an important tool for characterizing the biopharmaceutical quality of a product at different stages in the pharmaceutical product's life cycle.
- In early drug development, in vitro dissolution properties are supportive for choosing and evaluating formulation candidates for further development.

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- Dissolution is one of the critical tests used to release a finished drug product:

- **Ensures** that the performance of the finished drug product is consistent with pre-determined release rates of the API

It is useful to check

- Batch to Batch consistency
- Patch Stability change
- Production Batch Composition

Dissolution is very important when assessing changes (formulation, production site, scaleup etc)

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-USP Methods for Dissolution Test-

Apparatus	Description	Dosage Form
I	Basket	IR, DR, ER.
II	Paddle	IR, DR, ER.
III	Reciprocating Cylinder	IR, ER.
IV	Flow Through Cell	ER, Poorly Soluble API
V	Paddle over Disk	Transdermal
VI	Rotating Cylinder	Transdermal
VII	Reciprocating Holder	ER, Transdermal

IR= Immediate Release, DR= Delayed Release, ER= Extended Release.

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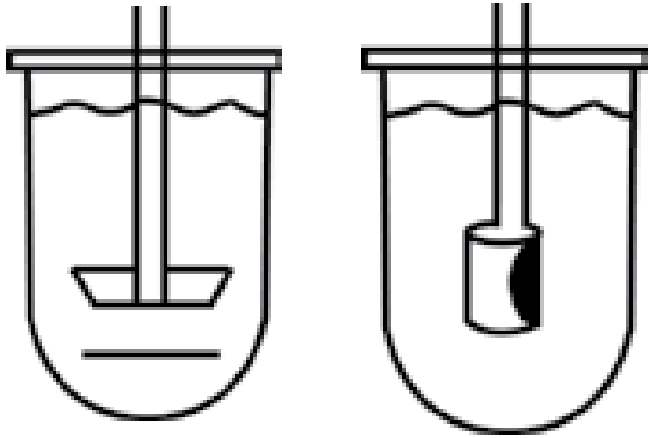
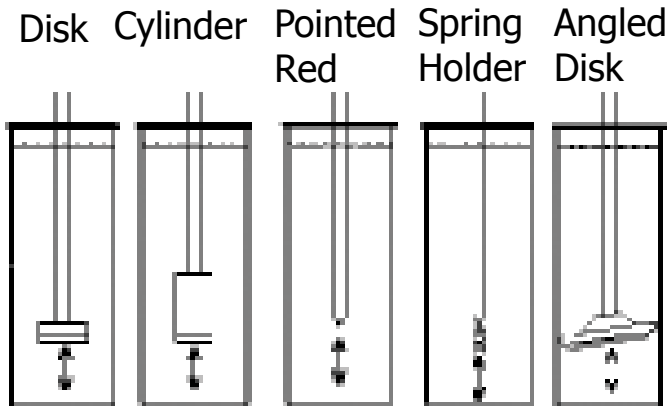
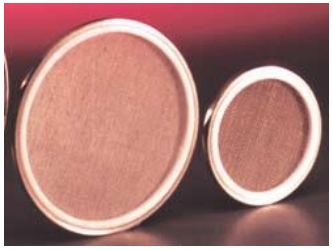
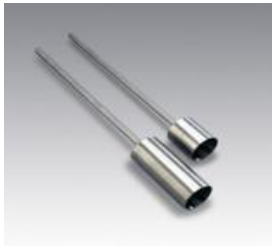
Dissolution for Transdermal Patch

USP Apparatus 5 (Paddle over the disk)
USP Apparatus 6 (Cylinder)
USP Apparatus 7 (Reciprocating holder)









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In vivo / In vitro correlation

- It is always a challenge to set dissolution test conditions to reflect in vivo/vitro skin permeation.
  - Drug release (dissolution) medium is different from skin character
  - In vivo absorption is controlled by not only patch formulation but also skin.
  - Normally permeation enhancer play a big role when applied on skin.

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Drug Release Test for TDDS (USP) -Example-1-

Transdermal Patch		USP Apparatus	Test Duration	Clinical Use
Nicotine	Test 2	VI	24 hr	24 hr
	Test 1	VII	24 hr	
	Test 5	VI	24 hr	
Scopolamine		VII	72 hr (3 days)	3 days
Clonidine	Test 3	V	168 hr (7 days)	7 days
	Test 2	VI	168 hr (7 days)	
	Test 1	VII	168 hr (7 days)	

Test duration of drug release test matches clinical use duration

Several test methods are listed in USP for one product. However, all tests are not required for the approval.

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Drug Release Test for TDDS -Example-2-

Name		USP Apparatus	Test Duration	Clinical Use
Nicotine	Test 3	V	4 hr	24 hr
	Test 4	V	16 hr	
Nitroglycerin		V	3 hr	12 hr
Buprenorphine		VI	24 hr	7 days
Fentanyl		VII	24 hr	3 days

Test duration of drug release test **does not match** clinical use duration

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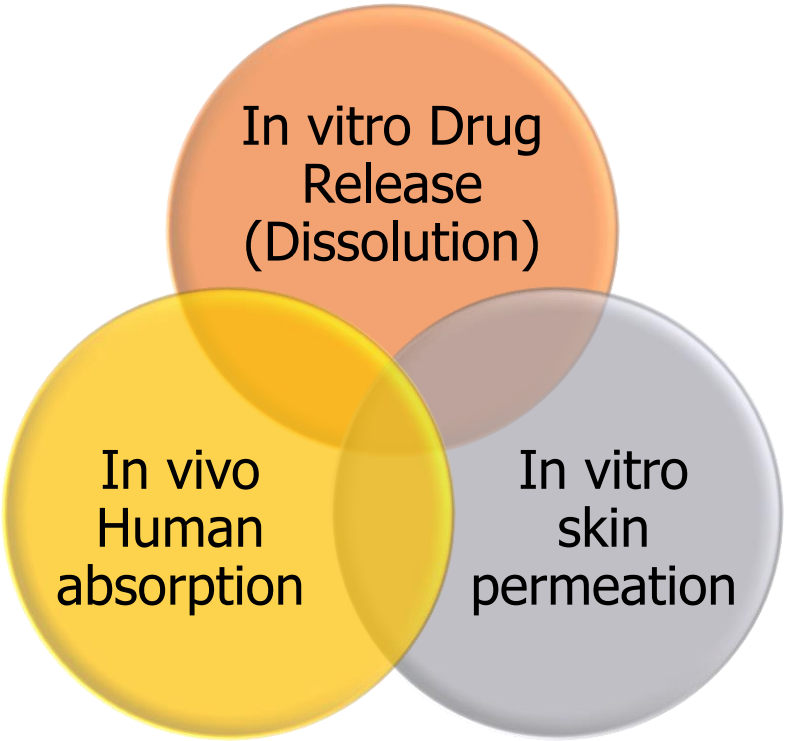
In vivo / In vitro correlation



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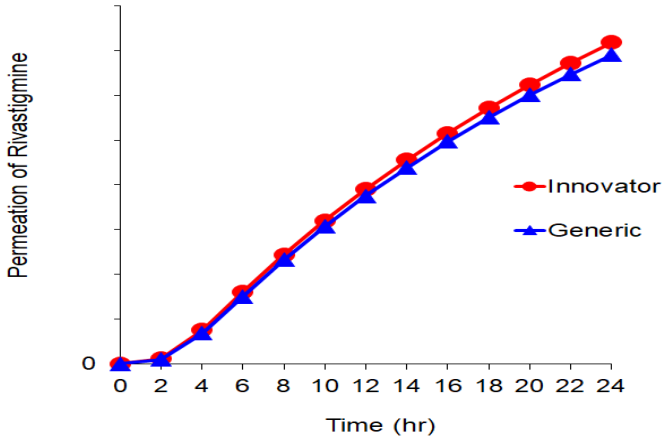
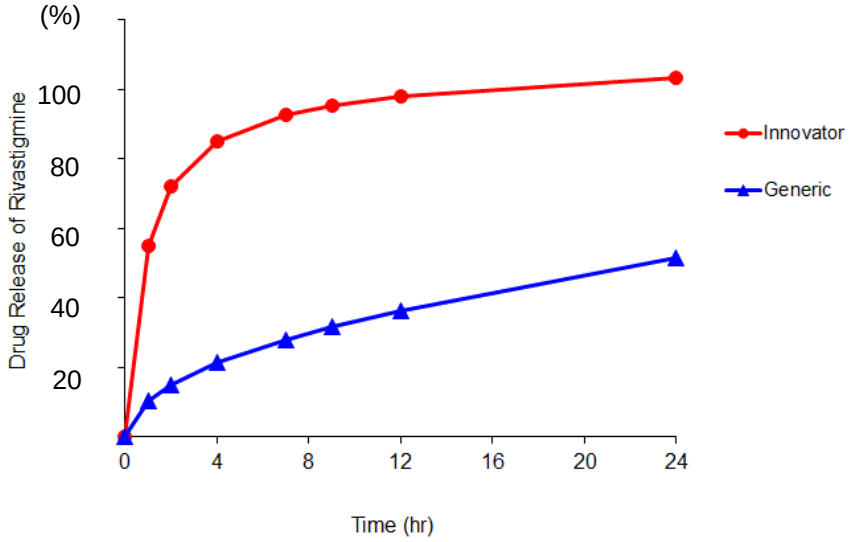
From Sparsha Laboratory - Rivastigmine case -

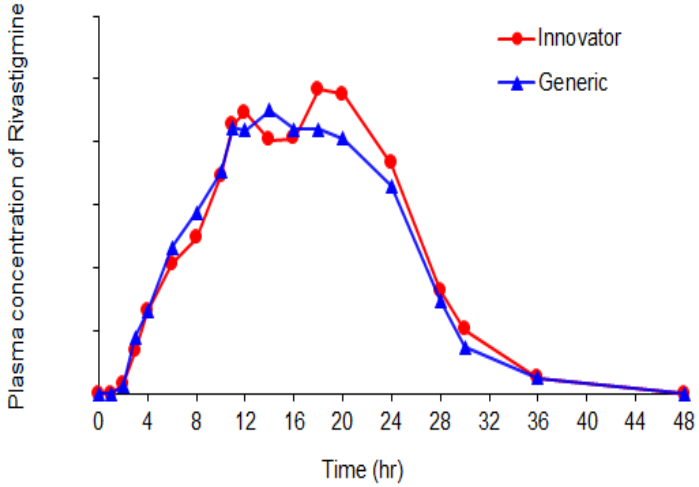
In vitro Human skin permeation



Drug release test



Human PK



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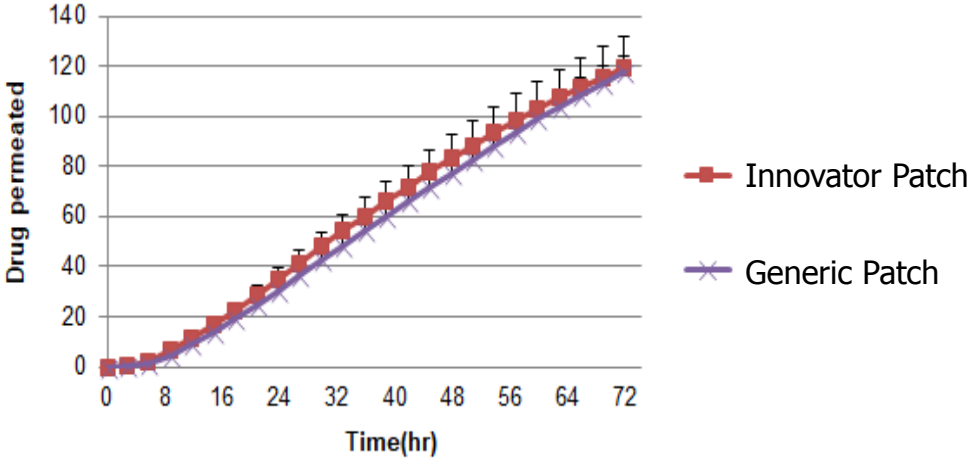
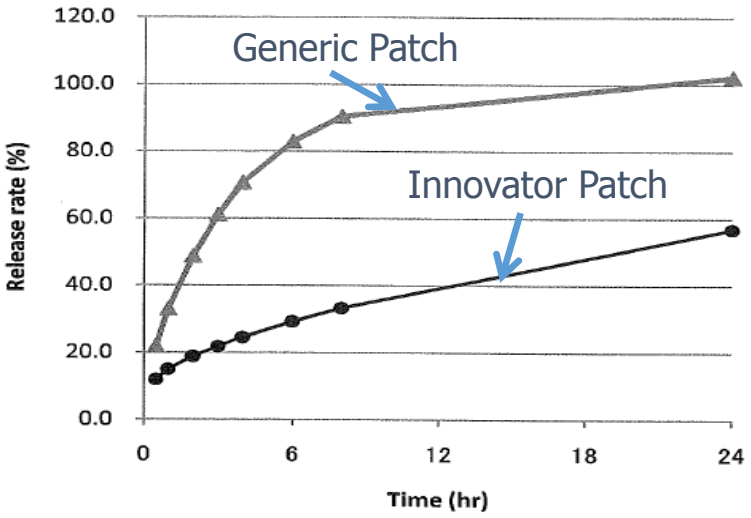
From Sparsha Laboratory - Fentanyl Case -

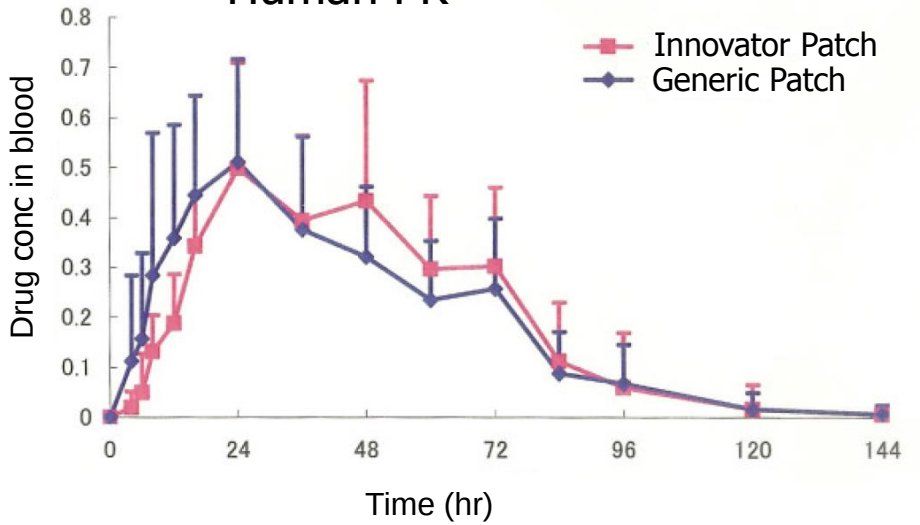
In vitro Human Skin Permeation



In vitro dissolution



Human PK



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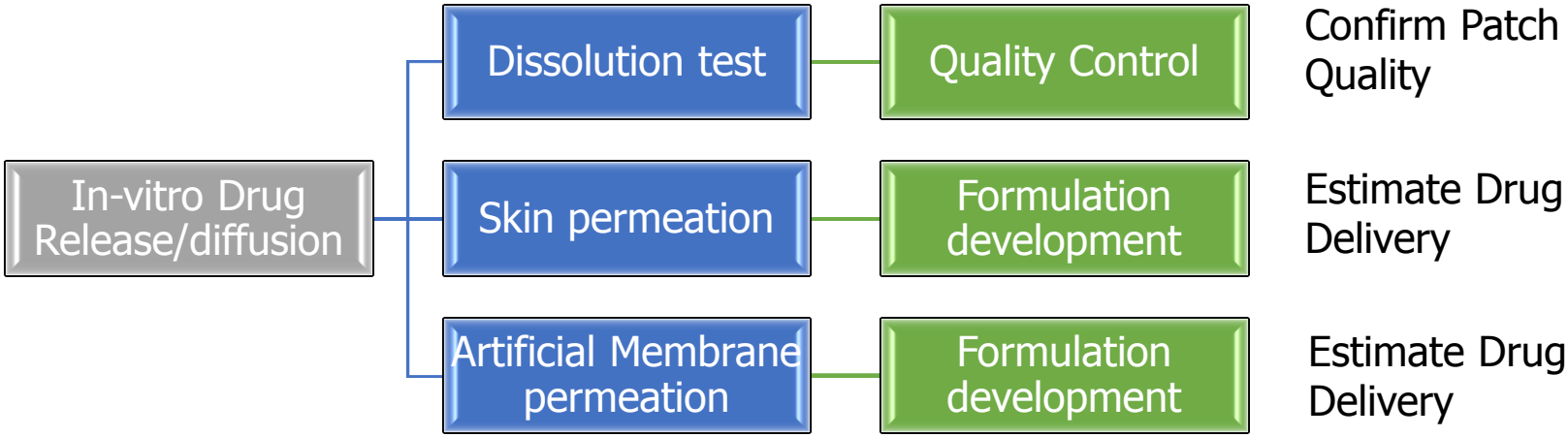
In vitro Drug Release/Diffusion



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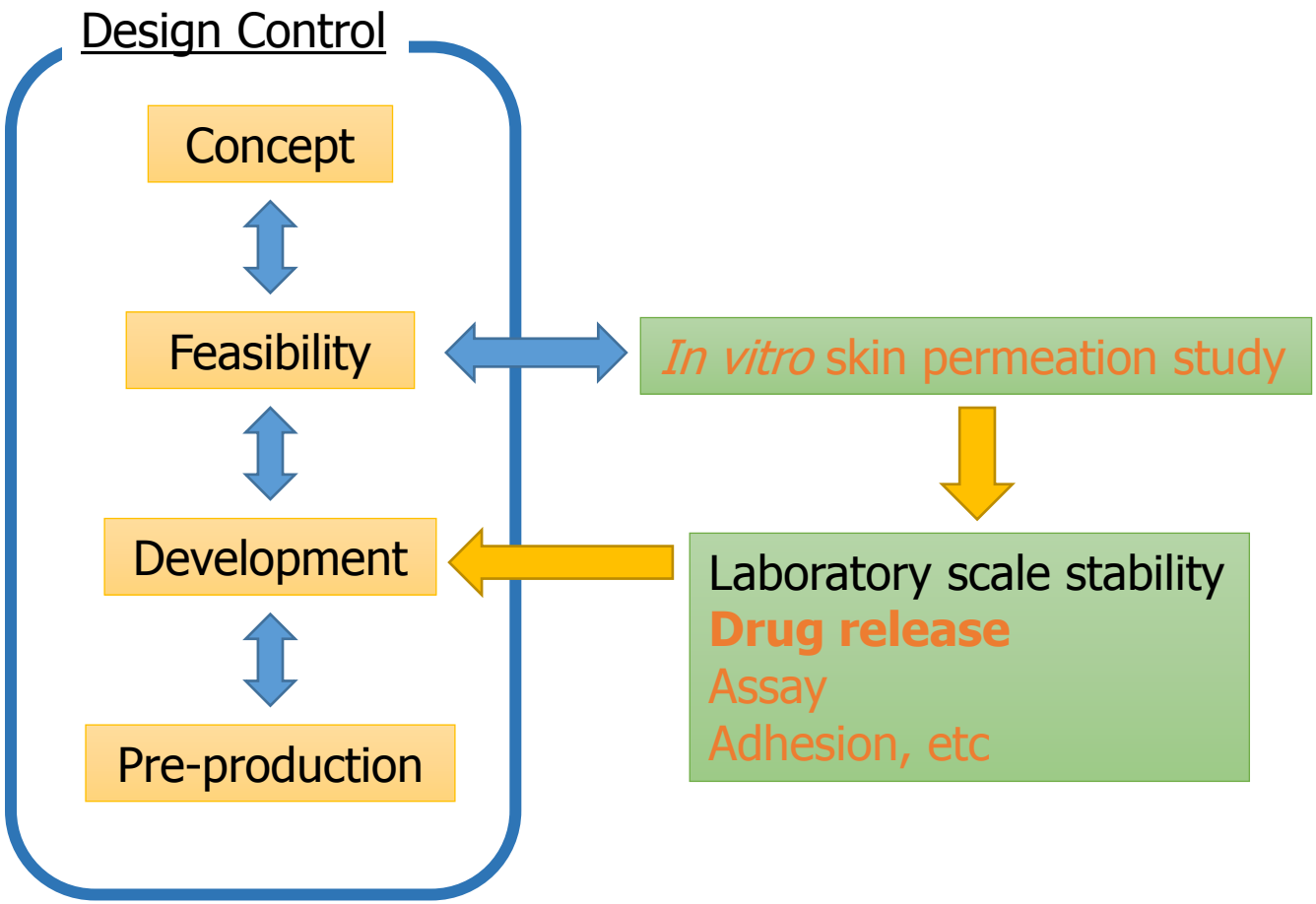
Dissolution Test on TDDS Formulation Development



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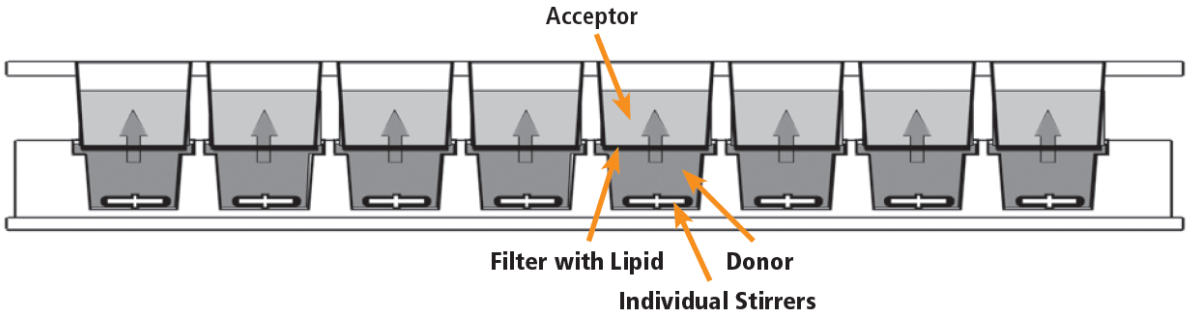
Artificial Membrane



1. Skin similar membrane (Ceramide like material membrane) will expect better correlation between in vivo/in vitro.
2. Well to well variation = contact between membrane and test sample
3. Higher drug delivery estimation
4. Cost is high

Future potential for dissolution test (Drug release test) as well as formulation screening.

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Challenges and Development

- The *USP* apparatuses produce good, reproducible results, yet some further modifications could improve the instruments' suitability.
- Dissolution test alone cannot estimate the actual in vivo percent of drug released and the rate of drug release from TDDS.
- Requirement of large volume of buffer for testing, reduce the optimality for the detection of low amounts of drug. Need to develop low-volume apparatus/instruments.
- Selection of suitable USP apparatus and method to carry out the dissolution studies depends on its sizes, shapes and strength (amount of drug).
- The differences between in vitro dissolution and in vivo release are caused by difference of dissolution media and skin characteristics.
- There is need to overcome the current challenges in dissolution study of TDDS to yield more correlative results with in vivo.
- Using artificial membrane could potentially mimic skin.

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TDDS as Combination Product

CGMP Compliance Expectations for Combination Product with Emphasis to TDDS as Drug-Device Combination Product

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What is a Combination Product?

Combination of 2 or more types of medical products:

- Drug + Device
- Device + Biologic
- Drug + Biologic
- Drug + Device + Biologic

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Types of Combination Products

- Three kinds defined in 21 CFR 3.2(e):
  - "Single-entity" (e.g., drug-eluting stent)
  - "Co-package" (e.g., first-aid or surgical kit, or a syringe packaged with vial of a drug)
  - "Cross-labeled" (e.g., certain light-emitting devices and light-activated drugs)

- Note that drug-drug combinations are "fixed dose combination products," not combination products under 21 CFR Part 3

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Under 21 CFR 3.2 (e), a combination product is defined to include:

1. **Single entity combination product**: A product comprised of *two or more regulated components* (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically or otherwise combined or mixed and produced as a single entity.

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2. **Co-packaged combination product**: *Two or more separate products packaged together in a single package or as a unit* and comprised of drug and device products, device and biological products, or biological and drug products.

3. **Cross labeled-combination product**: A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in does); or

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21 CFR Part 4 Combination Products are regulated as follows:

- **For drug products: 21 CFR parts 210 and 211 (TDDS)**
- **For device part: 21 CFR 820 (TDDS)**
- For biologics part: 21 CFR part 600-680
- For HCT/P component: 21 CFR 1271

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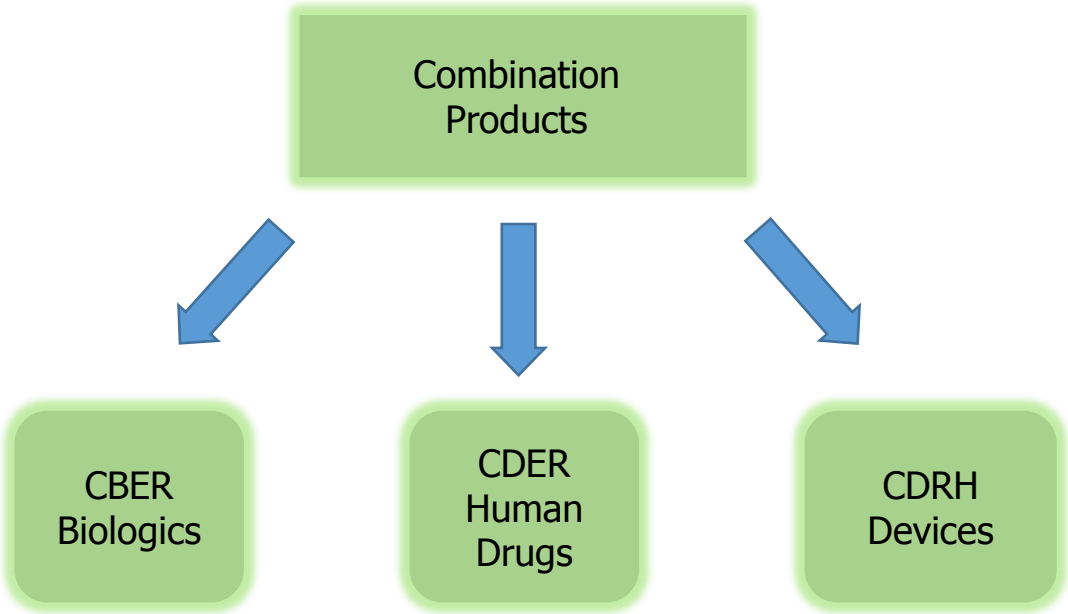
In the U.S. FDA, the Office of Combination Products is responsible primarily to assign the combination products to the appropriate FDA Centers based on Primary Mode of Action (PMOA)



Examples of CDER-led combination products:

-**Transdermal patches**

-Iontophoretic (ionic medicinal compounds) drug delivery patch and controller

-Pre-filled syringes

-Pre-filled autoinjectors

-Antibody-drug conjugates

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CGMP Requirements for Drug Product:

-211.84 Testing and approval or rejection of components, drug product containers, and closures
-211.103 Calculation of yield
-211.132 Tamper-evident packaging for over-the-counter (OTC) human drug products
-211.137 Expiration Dating
-211.165 Testing and release for distribution
-211.166 Stability testing
-211.167 Special testing requirements
-211.170 Reserve samples

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For TDDS, on top of CFR Part 210 and 211, the following CFR Part 820 Quality System Regulations are required:

820.20	Management Responsibility
820.30	Design Controls
820.50	Purchasing Controls
820.100	Corrective and Preventive Action

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Facility Assessment for TDDS
(as Combination Product ANDA)

TDDS with a drug PMOA will generally have a facility assessment by the following for compliance:

- CDER (Center for Drug Evaluation and Research)
- OPQ (Office of Pharmaceutical Quality)
- OPF (Office of Process and Facilities)
- CDRH (Center for Devices and Radiological Health)

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Final Guidance

Current Good Manufacturing Practice Requirements for Combination Products, January 2017

- Selection of CGMP operating system:
  - Combination product manufacturers can choose whichever they prefer among:
- 211-based streamlined approach
- 820-streamlined approach, or
- non-streamlined approach (comply with both sets of regulations)
  - PMOA does not determine or dictate choice

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Thank you