Critical Quality Considerations for Transdermal Delivery Systems

Scientific and Regulatory Advances for Generic Topical and Transdermal Product Development

Complex Generic Drug Product Development Workshop

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CDER | U.S. FDA

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

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A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


FDA
Patients expect safe and effective medicine with every dose they take.
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Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence in their *next* dose of medicine.

Overview

- Quality by Design for Transdermal System (TDS) Products
- Expectations for Extractables and Leachables
- Changes to Components Prior to Approval
- Adhesive Quality Tests
- Labeling Considerations

Quality by Design for TDS

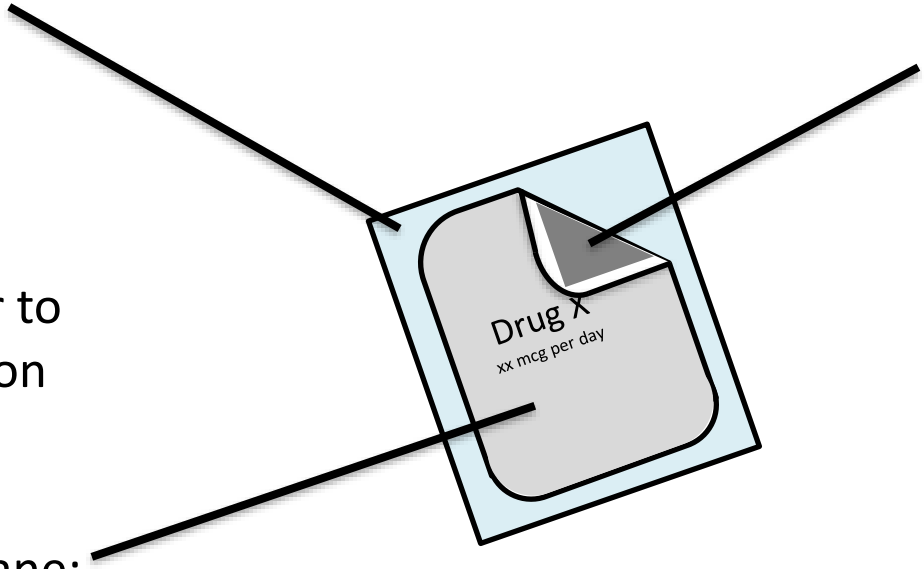
Design with the end user in mind

Clinical Concern	Quality Aspects
Adhesion to skin	• **Selection and quality control of raw materials**
Irritation/ Sensitization of skin	
Effectiveness/ Bioequivalence	• Uniformity *(robust manufacturing process)* • In vitro release testing • **Adhesive quality tests** • **Stability** *(Clinical studies typically are performed on fresh batches – not on aged batches)* – **Adhesive cold flow** – **Adhesive property change** – Drug crystallization – Delivery profile change – Drug-substance/excipient migration
Safety	• Impurities of toxicological relevance – Adhesive impurities (monomers, catalysts, crosslinkers, etc.) – **Extractables and leachables** • Residual drug *(accidental or environmental exposure, abuse)* • Heat influence *(e.g., application of a heat pack)* • **Proper labeling of each system**
Patient use	• **Release liner peel** • **Product design**

For discussion of some of the quality aspects not covered by this talk, please reference 2018's talk:
How to resolve current challenges with ANDAs for TDS slides and recording

Anatomy of TDS

Release liner:
- PET material
- May have coating
- Removed by patient prior to administration



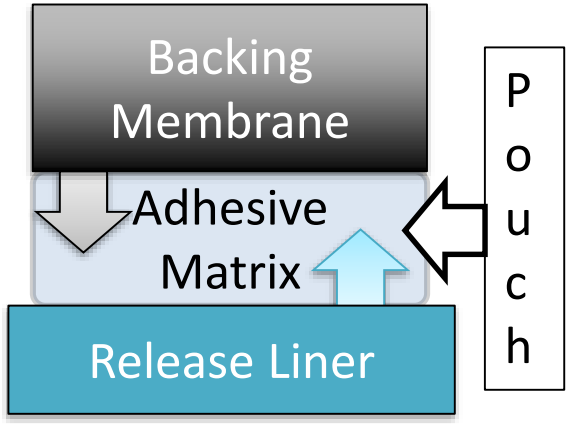
Adhesive layer:
- Contains drug (dissolved or suspended)
- May contain mixture of adhesive types and grades
- May contain additional excipients

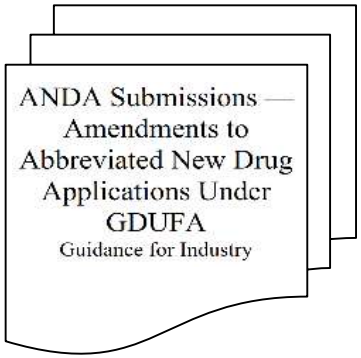
Backing membrane:
- PET/EVA materials
- May be occlusive
- Contains printed identifying label

TDS design may also incorporate:
- Multiple adhesive layers
- Internal membrane

Extractables and Leachables Studies

- Needed to demonstrate drug product safety
- Leachables may come from pouchstock, oxygen scavenger, slip sheets, release liner, backing membrane, and internal membranes
  - Impurities from adhesives or other excipients within the adhesive matrix are ***not*** leachables
- Lack of E/L studies or inadequate E/L studies may result in a **major deficiency**





Appendix A – Major Deficiencies, Section A(2)(o)

Expectations for Extractables Study

Goal: Identify potential leachables and demonstrate suitability of analytical methods to detect potential leachables

Critical Element	Agency Expectations
Pre-Identification of Potential Leachables	• Vendor literature/statements on impurities in drug product components • Discussion about which compounds are most likely to leach from drug product components

Solvent Selection and Extraction Conditions	• Selected extraction solvents should:
	  ○ cover a wide range of polarities
	  ○ include the solvent system used in manufacture of the drug product
	• Justification for extraction time, temperature, volume of solvent, and amount of component
	• A strong justification for extraction conditions is attainment of asymptotic levels of extractables

Analytical Methods and Identification of Extractables	• Multiple methods used to achieve detection of volatile, semi-volatile, and non-volatile organic compounds • Extractables designated as Confirmed, Confident, or Tentative as defined in USP <1663>

Expectations for Leachables Study

Goal: Identify and quantify leachables present in the adhesive matrix at release and during stability, using defined analytical thresholds.

Example of Inadequate Study Design

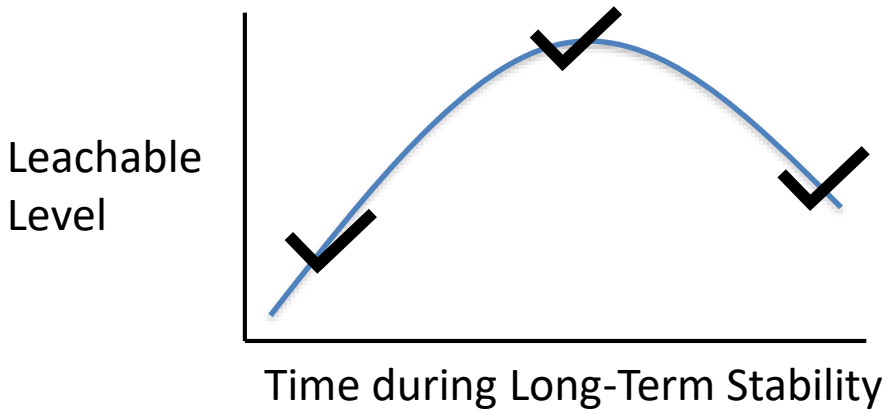
- Release liner not removed
- Extraction solvent is water
- No agitation during extraction
- Levels do not reach asymptote

Example of Adequate Study Design

- Release liner removed from system
- Extraction solvent mimics worst-case clinical conditions of skin
- Agitation during extraction
- Asymptotic levels obtained

Expectations for Leachables Study

Critical Element	Agency Expectations
Analytical Methods	• In general, methods agree with methods used for extractables study.
Number of Batches Used for Study	• Leachable studies performed using finished product from at least two exhibit batches.
Analysis During Stability	• Leachable studies performed at multiple time points during long-term stability studies.



Identification and Quantification of Leachables

- SCT = Safety Concern Threshold
  - Product-specific
- AET = Analytical Evaluation Threshold
  - Calculated using SCT
  - Limit of quantification should be less than AET
- Structural analysis of compounds present at levels > AET
- General equation for TDS (derived from USP <1664>):

$$AET\left[\frac{mcg}{system}\right] = \left(\frac{SCT\ [mcg/day]}{maximum\ number\ of\ systems\ /\ day}\right)$$

Assessment of Safety Considerations

- Any leachable present in the drug product at a level > SCT should be qualified for safety, considering local and systemic toxicity
  - Inadequate qualification of leachable present > SCT will result in a **major deficiency**
- SCT values for marketed TDS:

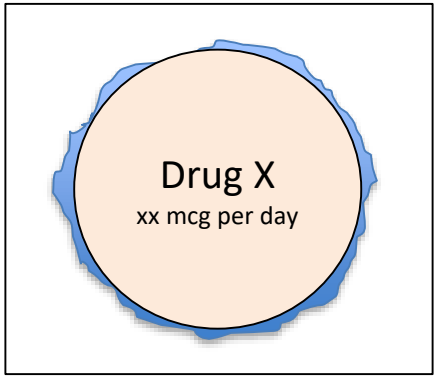
Drug Product	Product Type	Safety Control Threshold (SCT)
Buprenorphine	Transdermal system	1.5 mcg/day
Clonidine	Transdermal system	1.5 mcg/day
Diclofenac epolamine	Topical system	5 mcg/day
Estradiol	Transdermal system	1.5 mcg/day
Fentanyl	Transdermal system	1.5 mcg/day
Granisetron	Transdermal system	5 mcg/day
Lidocaine	Topical system	1.5 mcg/day
Methylphenidate	Transdermal system	1.5 mcg/day
Nicotine	Transdermal system	5 mcg/day
Rivastigmine	Transdermal system	1.5 mcg/day
Rotigotine	Transdermal system	1.5 mcg/day
Scopolamine	Transdermal system	5 mcg/day
Note: Follows approaches described in ICH M7 for genotoxicity assessment		

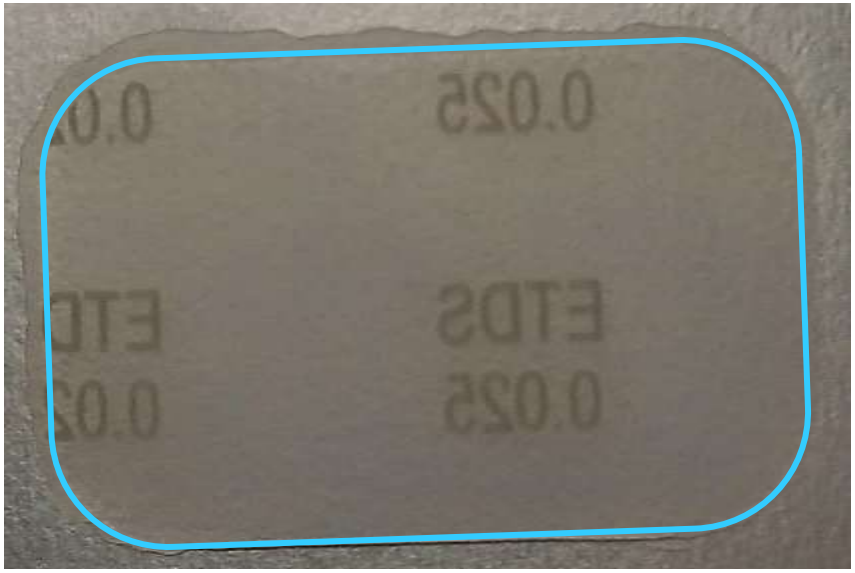
Changes to Components Prior to Approval

- Changes to components may be driven by vendor supply issues or by quality concerns
- Common changes proposed prior to approval include changes to pouchstock and release liner

Defining Cold Flow

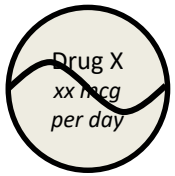
- The movement of adhesive beyond the edge of TDS or between the slit
- Poses risks to quality and patient use
  - Difficulty in removal from packaging
  - Potential for peel-off during wear (e.g., sticking to clothing)



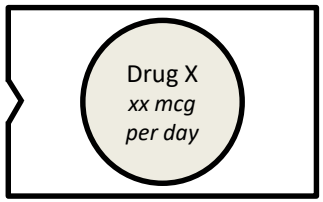


Change to Release Liner
Example 1: Patient Use

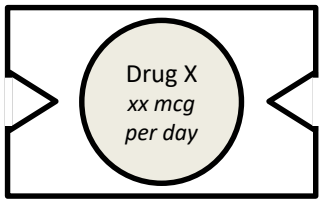
- Applicant proposed tear-able release liner design with notch in release liner
  - Design mitigates risk of cold flow protruding from slit
- Applicant requested to add second notch and make notches more apparent
- **<u>Quality data to support change:</u>** Diagram showing differences between exhibit batch design and commercial design



S-Cut Design



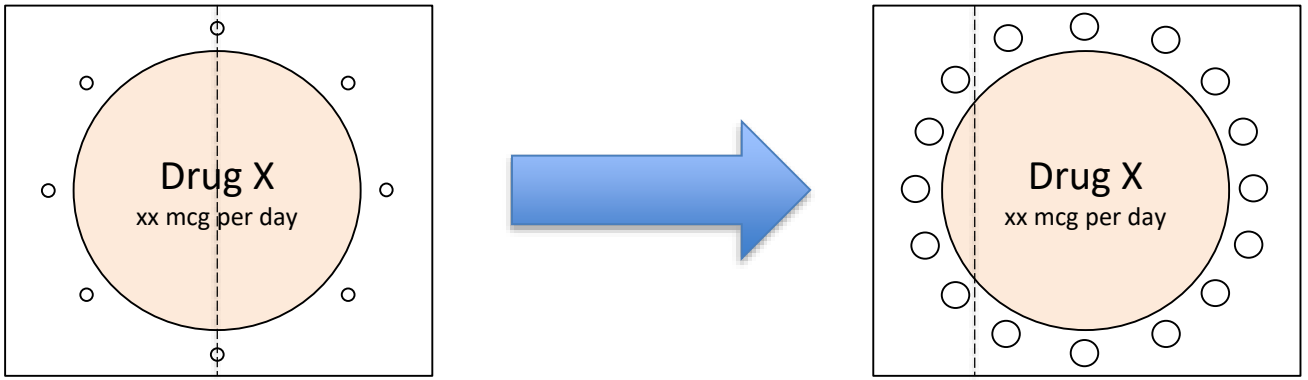
Tear-able Design
for Exhibit Batch



Tear-able Design
for Commercial Batch

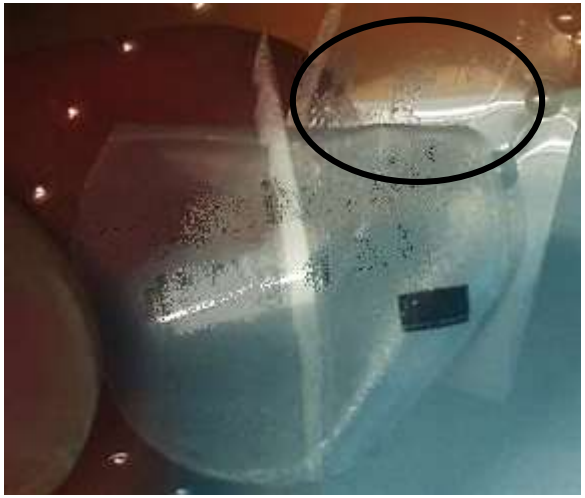
Change to Release Liner
Example 2: Cold Flow

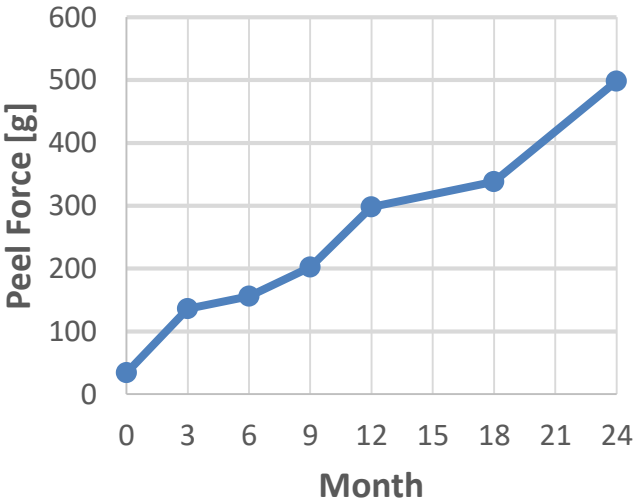
- Applicant observed significant cold flow during stability studies of exhibit batches
- Applicant proposed change to dimples in release liner to mitigate the risk of cold flow
  - Increase size of dimples
  - Increase number of dimples
- Applicant also proposed change to location of release liner slit
- **<u>Quality data to support change:</u>**
  - Manufacture of additional exhibit batch with accelerated and long term stability data demonstrating reduced cold flow
  - All quality documentation for additional exhibit batch



Change to Release Liner
Example 3: Release Liner Peel Force

- High release liner peel force poses risk to patient use
  - System may be difficult or impossible to remove
  - Adhesive transfer may occur
- Applicant proposed change in release liner material to mitigate risk of increasing release liner peel during shelf life
- **<u>Quality data to support change:</u>**
  - Manufacture of additional exhibit batch with accelerated and long term stability data demonstrating no increase in release liner peel force
  - All quality documentation for additional exhibit batch
  - E/L studies to support new release liner





<u>Release Liner Peel Force during Long Term Stability</u>

Changes to Components: Extractables and Leachables

- For a component change in an existing drug product previously qualified by extractables and leachables studies, a risk-based approach should be taken

Initial Risk	Extractables Study Required?	Comparable Extractables Analysis	Updated Risk
MODERATE	Yes	Similar	**LOW**
		Different	**HIGH**

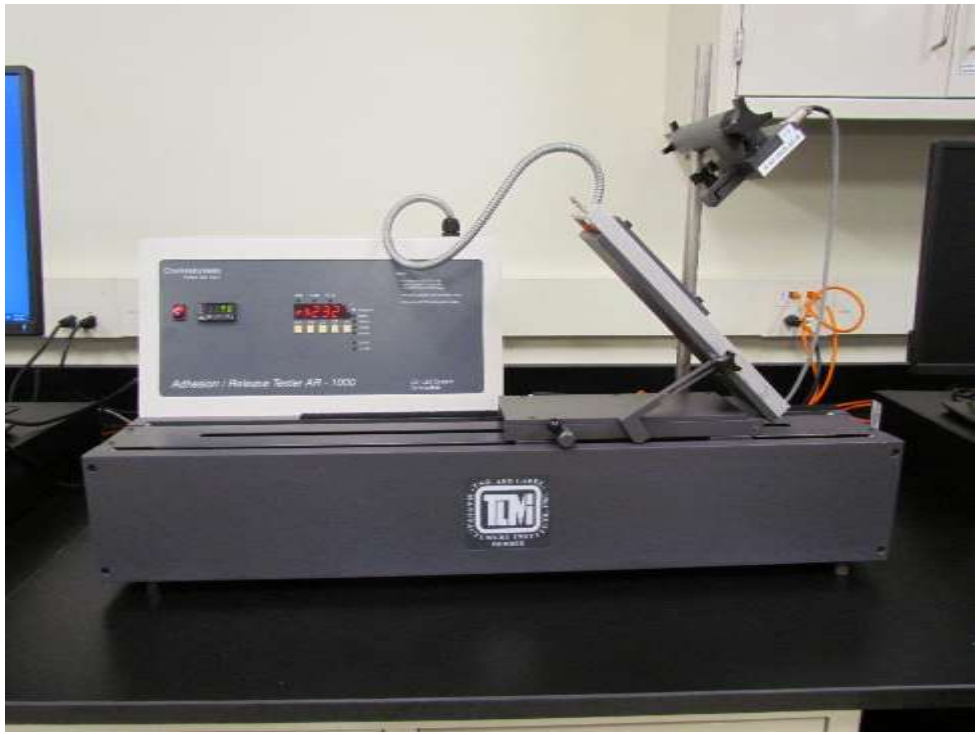
Adhesive Quality Tests

- Adhesive quality tests are tools for quality control
  - Peel adhesion
  - Release liner peel
  - Shear
  - Tack
- How we use this information
  - Ensuring consistency…
    - within a batch (*in-process testing*)
    - between batches (*finished product testing*)
    - upon aging (*shelf-life evaluation*)
    - between the clinical study batch and future commercial batches

Adhesive Quality Tests – Peel Adhesion

- ASTM D3330/D3330M is the standard

Method A: 180° Peel from Steel

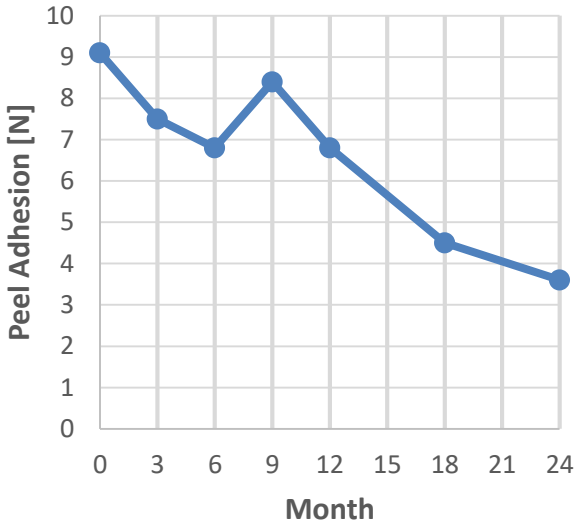


Method F: 90° Peel from Steel

Adhesive Quality Tests – Variation in Peel Adhesion

- Precision should be demonstrated by method validation
  - Maximum expected variation defined in ASTM D3330/D33330M
- Variability should be minimized during method development to ensure suitability of method as QC test

Trends in stability or differences between lots at release should not be attributable to variability in method



Peel Adhesion during Long Term Stability

Adhesive Quality Tests – Variation in Peel Adhesion

Example Deficiency:

We acknowledge that peel adhesion methods have inherent variability in the individual result obtained for a system. However, you are responsible for providing suitable methods to observe trending and lot-to-lot variability in critical quality attributes. For example, if any observed changes during stability for peel adhesion will be attributed to method variability, then the method is not suitable for its intended purpose.

We recommend you modify the peel adhesion method to reduce variability in the reported mean result.

Adhesive Quality Tests –
Sources of Variation in Peel Adhesion Method

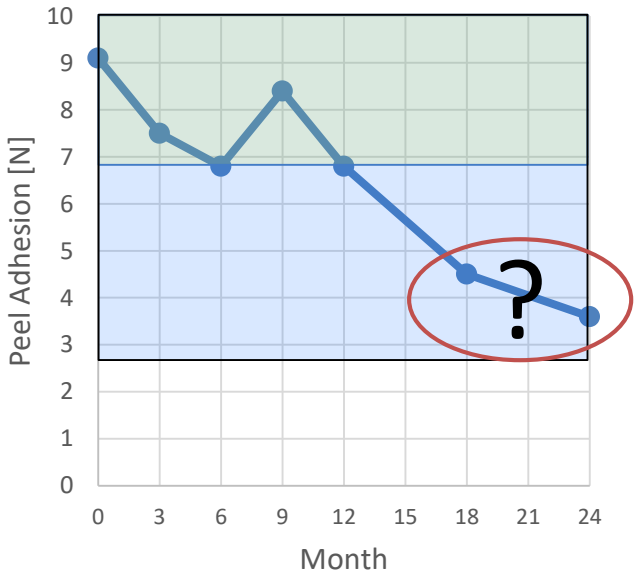
Sources of Variation	Mitigation Strategy Examples
Operator	• Training (set-up and calibration) • Define how to integrate the profile in method
Condition of test plate	• Method includes visual examination of any discoloration or scratches
Cleaning of test plate	• Method includes instructions for cleaning • Specify solvent in method
Storage of test plates	• Use of cloth between plates or a plate holder
Measurement rate	• Method specifies rate and angle
Dwell time	• Dwell time stated in method
Number of rolls	• Number of passes and direction specified in method
Roller specs	• Weight and size of roller specified in method
Presentation of Final Sample	• Check for bubbles after adhering sample • Method includes representative diagrams
Type of backing	• If foam backing, may need to add a stiff overlay tape
Presence of cold flow	• Investigate effect on peel adhesion if you observe cold flow during product development
Number of samples tested	• Precision increases as number of samples tested increases

Specimen Cutters

4.5 lb Roller

Adhesive Quality Tests – Acceptance Criteria

- Acceptance criteria should be a range
- Acceptance criteria should be justified by results for clinical batches at release
  - Not justified by stability data
- No assurance that trends on stability will result in product with similar product quality or in vivo adhesion



Labeling Considerations

- Identifying label on backing membrane
  - List drug name and strength
  - Easily readable
  - Durable
  - Green ink for fentanyl TDS
- Changes in ink composition or addition of new label on system should be supported by E/L studies or ink penetration studies

Section B(1), Transdermal Systems

Labeling Considerations

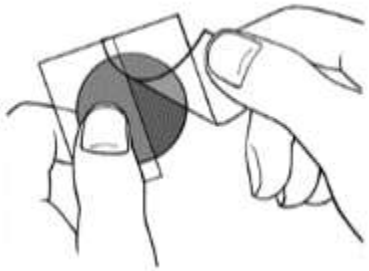
- Listing of inactive ingredients
  - Include release liner, backing membrane, and internal membranes

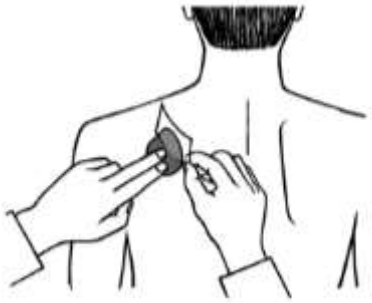
Each system is comprised of a siliconized polyethylene terephthalate (PET) release liner and two functional layers. Proceeding from the outer surface toward the surface adhering to skin, these functional layers are:

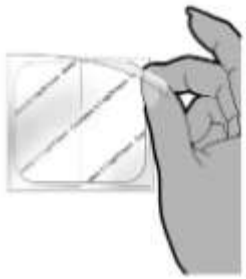
1) a transparent backing layer of ethylene vinyl acetate/polyethylene terephthalate (EVA/PET) film with green print; 2) a drug-in-adhesive layer containing fentanyl, polyacrylate adhesive, and isopropyl myristate. Before use, a siliconized PET release liner covering the drug-in-adhesive layer is removed and discarded.

Labeling Considerations

- Instructions for Use should accurately reflect generic product's design
  - For example, images should use generic design's shape, release liner design, and identifying label







Conclusions

- Adequate extractables and leachables studies are needed for pre-market approval and to support some post-approval changes
- Component selection and design are critical to achieving desired drug product quality
- Change in components prior to approval should be supported by quality data
- Development and validation of adhesive quality tests should demonstrate suitability of methods as quality control tools
- Labeling should accurately represent the proposed generic drug product
- Identifying label should include drug substance name and strength

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