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Improved Development and Regulation of Transdermal Systems

FDA Perspective on Safety Considerations with Transdermal Drug Delivery Systems

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Development & Regulation

- Several aspects to consider in transdermal system development that impact the performance of the product in clinical use
- Consider user needs along with commercialization aspects early in product development to avoid safety issues post-approval
- Some regulatory challenges with transdermal systems
  - emerging science
  - limited experience due to relatively small number of transdermal products

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Post-marketing Safety Issues

- Post-marketing surveillance to evaluate product safety
  - MedWatch reports of AEs
  - Product Quality complaints
  - Media reports
- Many issues identified by Regulators post-marketing related to safety and quality
  - AEs and death reported
  - Numerous product recalls, some interrupting market availability
  - DSCs, safety labeling changes, and other regulatory actions frequently occur post-approval with transdermal systems
- AEs reported tend to be due to over- or under-exposure to drug, as well as application site reactions

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Safety Issues

- Physical design aspects
- Active ingredients
- Inactive ingredients
- Indication for Use
- Patient Population
- Setting of Use
- Conditions of Use
- Labeling

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Physical Aspects Impacting Safety

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Total Drug Content

- Almost all transdermal systems contain far greater amount of drug than is intended to be delivered
  - Can increase exposure if transdermal system subjected to heat, overlays
  - Increase in drug exposure if transdermal system worn for an extended period of time
  - Disposal: exposure to used transdermal systems can pose risk for SAEs
- Important to reference total content in labeling, as well as on the carton, container, transdermal system and pouch
  - Primary strength expression should be on the dose delivered per unit of time (e.g. mg/hr, mg/24hr)

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Physical Design of System

- Handling area- many transdermal systems completely covered in adhesive/drug
- Caregivers may be exposed to drug when handling transdermal systems leading to systemic exp/AEs
- Size of transdermal system: can influence user's ability to manipulate properly during application

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What's in this transdermal system?

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Color and Markings

- Transdermal systems should be visible
- Transdermal systems should not appeal to children (avoid colorful designs and images)
- Should identify drug name (proprietary and established), dose delivered, and total drug content
  - Information should be visible throughout duration of wear

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Drug Exposure: Cmax and AUC

- Safety profile of a drug may differ when delivered transdermally
- For example, Norelgestromin/Ethinyl Estradiol exposes women to about 60 percent more total estrogen in their blood than if they were taking a typical birth control pill containing 35 micrograms of estrogen.
- However, the maximal blood level of estrogen (peak blood levels) is about 25% lower with Norelgestromin/Ethinyl Estradiol than with typical birth control pills."

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User Interactions with Transdermal Systems

Application & Removal

- Where to apply
- How many transdermal systems to apply
- How to apply
- How long to wear
- Activities of daily living: showering, swimming, exercise
- What to do if transdermal system falls off
- How to remove
- How and where to dispose
  - Trash, special disposal containers, flush

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Heat Exposure

- External heat sources shown to increase exposure to drug: rate and extent
  - Heating pads, blankets, tanning lamps, baths, saunas, hot tubs
- Fever also could impact drug exposure
- Death and SAEs reported in some cases where external heat sources applied to transdermal system
- Important to characterize the impact of heat exposure during development

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Adhesion

- Failed and partial adhesion of transdermal systems impact efficacy and may lead to serious safety issues
- Adhesion may differ under various conditions of use: exercise, site of application, patient population (adult, elderly, pediatric), water exposure, and so on.

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Adhesion Scoring

0 = ≥ 90% adhered (essentially no lift off the skin)

1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)

2 = ≥ 50% to < 75% adhered (less than half of the transdermal system lifting off the skin)

3 = > 0% to < 50% adhered but not detached (more than half of the transdermal system lifting off the skin without falling off)

4 = 0% adhered - transdermal system detached (transdermal system completely off the skin)

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Partial Adhesion Failures

- Safety concerns with partial adhesion failures (scored 1-3):
  - Patient may take precautionary measures such as taping or using overlays to secure the transdermal systems
  - Such measures may not have been evaluate to determine the impact on drug absorption. The use of overlays/tape can increase the heat at the application as well as alter skin permeability- both of which can increase drug exposure.
  - Partially adhering transdermal systems may also transfer to other individuals through close contact leading to systemic drug exposure and adverse events
- If you have significant proportions of transdermal systems exhibiting partial adhesion failures:
  - Investigate the root cause of partial adhesion failures and improve your adhesive if possible.
  - Consider studying the impact of overlays and tap on drug absorption so that these measures can be included in labeling for patients who notice transdermal systems peeling off the skin.

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Transdermal System Detachment

- Detached transdermal systems pose a risk to other people and animals
  - Affixed to other individuals or ingested by children and pets
- Serious Adverse Events and Death reported from secondary transdermal system exposures
- Designing transdermal systems to minimize detachments is critical
- Also, consider studying methods of securing transdermal systems (tape, overlays)
- Labeling should explicitly advise patients on what to do when transdermal systems detach
  - Locate detached transdermal systems, dispose of properly and use a new transdermal system
  - Re-application of detached transdermal system and secure with tape/overlay

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Labelling

- Patient and provider instructions for use impact safety
- Clear directives and comprehensive use information can improve the safe use of transdermal systems
- Safety issues can arise through absent information, and confusing instructions or diagrams
  - Test your instructions for use with intended users

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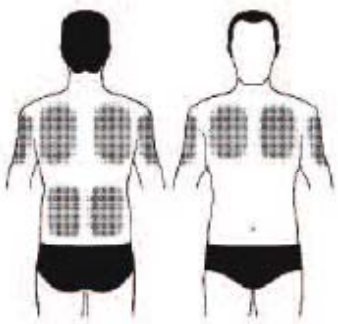
Patient Instructions

Diagram showing where to apply transdermal system



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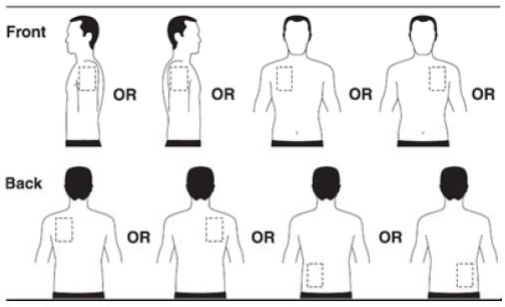
Revised application Instructions

Figure A:
Apply one patch to ONLY ONE of the following possible sites each day.



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Reducing User-Related Safety Risks

- Prospective risk assessments can identify risks with drug products, including transdermal systems
- Once risks identified, human factors studies can be conducted to characterize risks as well as identify strategies to reduce risks.
- Relying on controlled clinical studies or chemistry specifications to evaluate product performance and user interactions inadequate
  - Use-related information often not collected
  - Controlled environment may not mimic real-world use
  - CMC specifications may not correlate with clinical use
- Studies are generally small in size, short duration
  - Relatively small investment of resources can avoid the need to resolve issues post-approval

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Human Factors Studies

- Validate patient population can use transdermal systems in accordance with label instructions
  - Ideally, conducted pre-approval to prevent safety issues
  - May be requested post-approval if safety issues related to misuse are identified
- Usability studies: simulated or actual use
  - Assess patient interaction with transdermal systems
- Label comprehension studies
  - Assess patient understanding of instructions for use, risk/warning information, and so on

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General Advice

- Discuss development plans with FDA early- before your design is fixed
  - Experts in OND, ONDQA, and OSE may have advice to offer based on experience with other transdermal systems
- FDA also will review human factors protocols, if requested

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