Review Considerations for Transdermal Patches

Bhagwant Rege, Ph.D.
Office of Generic Drugs
Division of Chemistry I
Disclaimer

Opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or policies of the FDA.
Outline

• Provide definition and background on transdermal patches
• Discuss QTPP, CQAs, CMAs, CPPs, control strategy for transdermal patches
• Communicate Agency’s expectations in ANDA submissions
• Discuss sample deficiencies
USP 36 <1151>: Transdermal drug delivery systems (TDDS, “Patch”) are self-contained, discrete dosage forms that, when applied to intact skin, are designed to deliver the drug(s) through the skin to the systemic circulation.

**Systemic delivery**: The drug diffuses from the patch directly through the skin into the general circulation.

The activity of the TDDS is defined in terms of:
- the release rate of the drug(s) from the patch,
- the total duration of drug release from the patch and,
- the patch surface area.
TDDS (“Patch”)—Definition (cont’d)

The patch is applied to body areas consistent with the labeling for the product.

The patches are designed to provide drug delivery at a constant rate, such that a true steady-state blood concentration is achieved and maintained until the patch is removed (1-7 days).

As long as drug concentration at the patch/skin interface remains constant, the amount of drug in the dosage form does not influence plasma concentrations. The functional lifetime of the patch is defined by the initial amount of drug in the “patch” and the release rate from the “patch”.
FDA Approved TDDS Products

• Clonidine (Catapres®)
• Estradiol (Climara®)
• Estradiol/Norethindrone Acetate (CombiPatch®)
• Estradiol/Levonorgestrel (Climara Pro®)
• Fentanyl (Duragesic®)
• Methylphenidate (Daytrana System®)
• Nicotine (Nicoderm®)
• Norelgestromin/Ethinyl Estradiol (Ortho Evra®)
• Nitroglycerin (Nitro-dur®)
• Oxybutynin (Oxytrol®)
• Scopolamine (Scop®)
• Selegiline (Emsam®)
• Testosterone (Androderm®)

And Numerous Generic Products
Advantages and Disadvantages

Advantages:

- Avoidance of gastrointestinal drug absorption difficulties (pH, enzymatic activity, and drug-food interactions)
- Noninvasive
- Patient compliance
- Sustained or controlled drug delivery over extended periods; Maintenance of constant therapeutic drug levels,
- Drug therapy may be terminated
- Identified at anytime, and
- The potential for reducing some side effects generally associated with high peak serum drug concentrations observed after an immediate release dosage form.

Disadvantages:

- Natural limits of drug entry imposed by the skin’s impermeability (MW <500, narrow log P (partition co-efficiency) range and etc.)
- Limitation of drug level to be administered (Daily Systemic Dose: NMT 20 mg)
- Skin irritation
- Safety Issues (Residual Drug in Patches after use; Dose “dumping”).
- High cost
Types of TDDSs

- Reservoir Systems

Reservoir Systems consist of three major components: the drug reservoir, the rate-controlling membrane and the adhesive. Typically, the drug reservoir contains the drug and excipients.
Types of TDDSs

- Matrix System (Drug-in-Adhesive System)

**Matrix System** - the drug is in the adhesive. The adhesive performs the roles of formulation excipient (rate controlling) and adhesive. In addition, the matrix may contain permeation enhancer, solubilizer, crystallization inhibitor, plasticizer etc. The other components include backing membrane, release liner and an optional overlay.
Development of Generic TDDS

- A structured development program incorporating the following QbD elements is highly recommended
  - Quality Target Product Profile (QTPP): Begin with end in mind
  - Critical Quality Attributes (CQAs)
  - Product and Process Understanding: Identification of Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs)
  - Establish a comprehensive control strategy involving input material controls, in-process controls (process parameters and intermediates), and finished product controls
Key Considerations for QTPP: Analysis of RLD

• RLD Label
  – Description
  – Dosage Form and Strength
  – Dosage and Administration
  – Clinical Pharmacology
  – Warnings and Precautions
  – Adverse Reactions
  – Indications and Usage
  – How Supplied/Storage and Handling
  – Special “In use” conditions or instructions

• Physicochemical and Biopharmaceutical Analysis
  – Multiple batches including near expiration batches
  – Appearance, assay, CU, impurities, in vitro flux, dissolution
  – Special considerations: Residual monomers, penetration enhancer content
# QTPP for TDDS

<table>
<thead>
<tr>
<th>QTPP Element</th>
<th>Target</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Transdermal patch</td>
<td>Pharmaceutical equivalence requirement: same dosage form as RLD.</td>
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<tr>
<td>Route of administration</td>
<td>Transdermal</td>
<td>Pharmaceutical equivalence requirement: same dosage form as RLD.</td>
</tr>
<tr>
<td>Strength</td>
<td>Same delivery rate (Residual Drug consideration)</td>
<td>Pharmaceutical equivalence requirement: same dosage form as RLD.</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Meet Bioequivalence requirement</td>
<td>Bioequivalence requirement.</td>
</tr>
<tr>
<td>Stability</td>
<td>At least 24-month shelf-life stored at room temperature</td>
<td>Equivalent or better than the shelf-life of RLD.</td>
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</table>
# QTPP for TDDS

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<th>QTPP Element</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug product quality attributes</strong></td>
<td>Physical attributes (appearance, size, shape)</td>
<td></td>
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<tr>
<td></td>
<td>Patch Performance (adhesion, cohesion, etc)</td>
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<tr>
<td></td>
<td>Identification</td>
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<td></td>
<td>Assay</td>
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<td>Degradation products</td>
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<td>Residual solvents/monomers</td>
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<td>Content homogeneity</td>
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<td></td>
<td>Drug Release</td>
<td></td>
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<tr>
<td></td>
<td><strong>Patch Performance</strong> (adhesion, cohesion, etc)</td>
<td>Pharmaceutical equivalence requirements: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).</td>
</tr>
<tr>
<td><strong>Container closure system</strong></td>
<td>Suitable container closure system to achieve the target shelf-life and to ensure integrity during shipping.</td>
<td>Requirement to assure product quality over the shelf-life of the drug product.</td>
</tr>
<tr>
<td><strong>Administration/ concurrence with labeling</strong></td>
<td>Same as RLD</td>
<td>Information provided in the RLD labeling.</td>
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CQAs

- A CQA is a physical, chemical, biological or microbiological property or characteristic of output materials including finished drug product that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

- Criticality is dependent on severity of harm to the patient

- Assay, Uniformity of Dosage Units, Impurities, Drug Release, XRD for polymorph control, Particle size (distribution), Cold flow, Assay of drug in cold flow, Microbial Test, Residual Solvents, Residual Monomer, Enhancer (Assay and Uniformity of Dosage Units), Adhesion Test (Peel Test, Peel from Liner Test, Probe Tack), Cohesion Test (Shear)
In-Vitro Flux Studies

- Key tool in assessing delivery rate of transdermal patch and evaluate effect of CMAs on CQAs

- Factors to be considered
  - Type of diffusion cell (e.g. Franz diffusion cell)
  - Type of membrane (human cadaver skin, animal skin or synthetic)
  - Receptor fluid, stirring speed, temperature etc.

- Sponsors should provide data on how in-vitro flux studies were used to select formulations for bioequivalence studies such as
  - Effect of API particle size/polymorphism
  - Effect of penetration enhancers
  - Effect of adhesive ratios / contents

- In-vitro flux studies help to better define CQAs that need to be monitored or controlled such as particle size, polymorphism, adhesive ratios/content or penetration enhancer content
**In-Vitro Flux Studies**

Effect of exaggerated in-use conditions such as external heat, steam, water exposure etc. from RLD label on patch performance should be evaluated using *in-vitro* methods

ANDA product should give equivalent performance as RLD

Please refer to the FDA response to the CP 2012-P-0932 (see link below) for additional information.

http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0932-0003
Product and Process Understanding: Experimental Approaches

• Trial and error: Should be avoided

• One-factor-at-a-time (OFAT)
  – OFAT approach may miss important interactions between different material attributes and/or process parameters
  – requires more runs for the same precision to estimate effects compared to DOE
  – may not give optimal settings of factors

• Design of Experiments (DOE)
  – A structured, organized method for determining the relationship between factors affecting a process and the output of that process
  – Multivariate experiments may lead to establishment of design space that must be verified at commercial scale

Whatever approach is chosen, the information should be able to support conclusions on CMAs/CPPs/CQAs and control strategy
Critical Material Attributes (CMAs)

API
- Particle size / area
- Polymorph
- Impurities
- Solubility in formulation matrix

Pressure Sensitive Adhesive
- Adhesive type
- Viscosity
- Ratio (if mixture is used)
- Molecular weight
- Residual monomers

Delivery rate
Crystallization
Impurities
Delivery rate
Adhesion
Cohesion (cold flow)
Irritation / sensitization
Residual drug
Assay / Impurities

Permeation Enhancer
Crystallization Inhibitor
Rate Controlling membrane
Solvent

Delivery rate
Crystallization
Assay / Impurities

Backling membrane
Release liner

Patch integrity / flexibility
Critical Process Parameters (CPP) — Drug-in-adhesive System

Manufacture of the Drug-Containing Adhesive Mass
- Compounding process of adhesive, enhancer, other excipients and API

Potential CPPs: stirrer speed, vacuum.

Process Challenge/Scale-up: homogeneity/BUA of API and solid content; establish mixing speed, time

Manufacture of Drug-Containing Laminate
- Coating, drying and laminating

Potential CPPs: machine speed and pressure, temperatures at various drying tunnel,

Process Challenge/Scale-up: coating speed and temperature; laminator speed/pressure, roll size limit
Critical Process Parameters (CPP) - Drug-in-adhesive System

Slitting/Die-cutting

The drug-containing laminate is cut longitudinally into narrow rolls and then is unwound from the roll and cut into the individual TDDS.

Potential CPP: Slit width, die dimension, machine speed

Packaging

The individual TDDS is placed between two layers of packaging material and the packaging material is sealed around the edges.

Potential CPP: sealing temperature
Control Strategy
- From the Beginning to the End

**Input Material Control**
Establish controls on identified CMAs such as viscosity of adhesive solution, polymorphism of API (XRD) in addition to compendial controls or standard quality controls.

**In-Process Controls and Monitoring**
Establish rational controls on identified CPPs and process intermediates (e.g. coat weight, slit width)

**Finished product controls**
Establish controls on CQAs such as particle size and polymorphism of dispersed API in addition to compendial or standard quality controls
Stability Expectations

- **Three** lots of drug product manufactured from three distinct laminates, where each lot of laminate is made using different combination of sources of API/adhesives/backing and/or other critical elements in the patch.
- When the product contains multiple strengths, it is not necessary to produce three different laminates for each strength; same three laminates can be used to cut different strengths; bracketing may be possible.
- Batch size: 10% of commercial batch size or 25,000 patches whichever is greater for at least 2 batches, third batch can be smaller.
Sample Deficiencies

• API
  – You have indicated that you could not find any information on polymorphs of API. However, literature search indicates several references to polymorphs of API, both anhydrous and hydrate having different solubilities and melting points. Please characterize the polymorph used in your product. Please provide rationale for your chosen polymorph.
  – Please provide solubility of the API in formulation components. Please clarify if the API is soluble or dispersed or both in the matrix. What is the ratio of dissolved API to dispersed API? How will you insure that the ratio stays constant from batch to batch and throughout the shelf life of the product?
  – Please provide particle size control for the dispersed API as it can affect drug delivery rate from the system.
Sample Deficiencies

• Excipients
  – You have provided no data other than in vitro flux study on how you optimized crystallization inhibitor content. Please provide supporting XRD or DSC data to indicate that the optimized crystallization inhibitor is able to keep the API in dissolved state throughout the shelf life. Please also provide additional information on solvent used in the drug product manufacture and its impact on crystallization potential.
  – You have indicated that you have optimized the ratios of high and low molecular weight adhesives for optimum adhesion and minimal cold flow potential. Please provide supporting experimental data.
  – Please provide in vitro flux studies used to optimize the level of penetration enhancer.
Sample Deficiencies

• Characterization
  – Please provide characterization of cold flow potential of your product including cold flow weight and amount of API in cold flow. If significant amount of API is found in cold flow, we may initiate a safety consult. We ask that you propose suitable test and specification on cold flow.

  – The Agency requires evidence that the formulation of a generic product is not less safe than the RLD. We acknowledge that it is possible that different transdermal formulations of the same drug may have different responses to heat and/or under other “in-use conditions”. The RLD labeling states that “Contact with water while bathing, swimming or showering will not affect the patch”. To ensure that the RLD labeling with respect to heat and/or other in-use conditions are applicable to the ANDA product, the ANDA applicant should provide information about the formulation performance to ensure that the sensitivity to heat (or other “stress conditions”) of the generic product is not more pronounced than that of the RLD. You may design and provide an in vitro study (e.g., skin flux permeation study with “heat” or other “stressed” conditions to mimic certain in-use conditions) to compare in vitro skin permeation flux data to the RLD at normal and elevated temperatures. If the generic product was not more sensitive than the RLD, it would be acceptable. Such in vitro data would assure that the proposed generic TDDS product would not create a greater risk when exposed to heat (or under in-use conditions) than the RLD. Please refer to the FDA response to the CP 2012-P-0932 (see link below) for additional information.

http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0932-0003
Sample Deficiencies

• Manufacturing Process and controls
  – Please justify the range for laminator speed and pressure in your commercial batch record. The proposed range is outside of the range studied for your development batches.
  – Please clarify how you have optimized the coating speed, drying time and temperature.
  – You have indicated that the equipment proposed for use in commercial batches and those used in exhibit batches are of similar design and working principles but higher capacity. Please explain how you will adjust the critical process parameters for each unit operation to get product with consistent quality from batch to batch.
  – Please provide a list of critical process parameters (CPPs) for each unit operation with justification. How are these parameters controlled and monitored during batch manufacture?
Summary

• TDDS are complex and expensive drug products
• A structured development program incorporating QbD elements is highly encouraged
• The applicants should demonstrate product and process understanding such that impact of CMAs and CPPs on drug product CQAs is clearly identified
• The applicants should propose a comprehensive control strategy derived from the conclusions of product / process development
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