New Approaches and Optimization of Methods for BE Assessment of Topical Drug Products

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U.S. Pharmacopeia Meeting Center, Rockville, Maryland, USA, March 11-13, 2013
BIOAVAILABILITY

Systemically absorbed products

...... the rate and extent to which the active ingredient or moiety is absorbed from the drug product and becomes available at the site of action.

Products not intended to be absorbed

...... may be assessed by (surrogate) measurements intended to reflect the rate and extent to which the active ingredient or moiety becomes available at the site of action.

21 CFR 320.1(a)
Products Intended to be Absorbed into Systemic Circulation

- Surrogate measures justified by the presumption that concentration of drug in blood stream is in equilibrium and reflects the concentration at site of action
- Relationship between effectiveness and systemic blood concentrations of drug implied

Topical Products Not Intended to be Absorbed into the systemic circulation

- Surrogate measures cannot be justified on same basis as for drugs intended to be absorbed into the systemic circulation
- No such relationship expected
### Products Intended To Be Absorbed Into Systemic Circulation

- Methodology well established
- Statistical assessment of data well established
- Regulatory requirements based up $C_{\text{max}}$ and AUC falling within prescribed limits of CI of 90% and relative means of test to reference being within 80-125%

### Topical Products Not Intended To Be Absorbed

- Methodology under development
- Statistical assessment yet to be defined
- Regulatory requirements?

*except for topical dermatologic corticosteroids where the FDA Guidance requires that Locke’s method, which provides an exact confidence interval from untransformed data, be used.*
• Determines the amount of drug permeated into the *stratum corneum*

• Utilizes adhesive tape strips

• Relatively non-invasive

• Removes layers of *stratum corneum*
Tape stripping process

• Initial TS methodology outlining the bioavailability/bioequivalence protocol for topical formulations intended for local and/or regional activity, published in a draft guideline

• Subject to criticism which resulted in its withdrawal, mainly due to a number of limitations, in particular the sources of variability and control
• In 2002 FDA withdrew the guidance - major concerns raised regarding the reproducibility of the DPK method between laboratories.

• The latter concern was based on contradictory results generated by two reputable independent laboratories regarding the BE assessment of tretinoin gel products.
• Adequacy of the DPK method to assess topical products that did not target the SC?

• Differences in Protocols used by each of the laboratories?

• Differences in the actual stripping procedures?

• Differences may have been due to lateral spreading of the formulations?
• Large numbers of subjects necessary to achieve a statistical power greater than 80%, - inherent variability of the method.

• Additional sources variability due to the inconsistency in the amount of SC adhering to each tape strip?

• Variability in the amount of drug present on the discarded tape strips?

• Variability in the effectiveness of the cleaning procedure
Additional concerns/issues in existing methodology

• Trial-and-error approach taken to determine the time points at which TS should take place

• Amount of time and effort required to carry out the procedure

• Variability in SC characteristics, especially thickness of the SC, between individuals not taken into account
Further Concerns - Post-guidance withdrawal

Appropriateness of using parameters such as AUC and Amax - parameters derived from the principles of oral pharmacokinetics?

- After topical application of a drug, concentration found at the “site of action” is determined primarily by SC penetration and processes such as partitioning, diffusion and keratin binding.
- In contrast, when using the oral route, the plasma concentration vs. time profile obtained is controlled by the processes of absorption, distribution, metabolism and elimination.
When the topical product is applied, the penetration process begins and then at some time after application, the residual formulation is physically removed.

When using the oral route, (in the case of an immediate release formulation) absorption occurs until the dosage form is depleted, after which elimination processes start to dominate.

Oral and topical routes should thus have very different pharmacokinetic profiles?
Re-evaluation and Optimization of the TS Method

Novel approach (Herkenne et al*)

- Instead of totalling the amount of drug found in the SC, a profile is obtained which describes the amount of drug present at varying depths of the SC.

How long should the dose be left on the application sites prior to skin stripping?

- The choice of dose duration has generally been unsubstantiated.

- Sampling when the concentration of drug in the SC is at steady state is likely to mask differences in formulations, thus it is important to have a validated method of ensuring that the chosen dose duration falls on a sensitive part of a dose – response relationship, such as a plot of the dose duration vs. drug penetration profile.

- In order to determine a dose duration which will provide the necessary discriminatory power to identify significant differences or equality between products, the approach employed in the FDA HSBA guidance was used.
Determination of ED$_{50}$

- Perform a pilot study and use the $E_{\text{max}}$ model to determine the dose duration where the maximum sensitivity can be expected – i.e. the ED$_{50}$.

i.e. carried out at the most sensitive part of the dose-response curve
Determination of Dose Duration

- Pilot study required to determine dose duration.
  - $E_{\text{max}}$ model - most discriminatory dose duration

$$E = E_0 + \frac{E_{\text{max}} \times D}{ED_{50} + D}$$

where $E =$ effect elicited
$E_0 =$ baseline effect in the absence of ligand
$E_{\text{max}} =$ maximum effect elicited
$ED_{50} =$ dose duration (D) at which effect is half-maximal
Tape stripping for the bioequivalence assessment of a clotrimazole topical dosage form
Dose Duration Study Design

- Single phase sequential design, n =10 human subjects
- 8 (2 x 2 cm) sampling sites on the volar aspect of the left forearm
- 1 site as a blank and remaining 7 sites for product application
- Approximately 15 mg Canesten® Topical cream applied to each application site at time zero
- Each site exposed to the cream for a different dose duration (0.25, 0.5, 1, 2, 4, 6 or 8 hours respectively)
- The residual formulation was removed at the end of each DD and sites tape stripped
Normalisation of *stratum corneum* thickness

- The blank site also underwent TS, but in addition, TEWL measurements were taken after each strip in order that the thickness of each subject’s SC could be calculated.

- After TS, all tape strips analysed for drug content and a profile of dose duration vs AUC plotted and the ED$_{50}$ determined.
Transepidermal water loss (TEWL) measurements

- TEWL measurements were taken at the blank site only and used to determine SC thickness/subject.

- Stratum corneum thickness differs between individuals – hence, normalization necessary - measure transepidermal water loss (TEWL):

\[
\frac{1}{J} = \frac{1}{\text{TEWL}_x} = \frac{H-x}{K.D.\Delta C}
\]

- H can be determined by the x-intercept of the plot \( \frac{1}{\text{TEWL}_x} \) vs. x.

Calculation of AUC

- Before the dose duration profile could be constructed the extent of CLZ penetration occurring at each dose duration has to be determined.
- This was done by calculating the AUC (using the trapezoidal rule) of the curve obtained when the amount CLZ per tape strip was plotted against relative SC depth.
The data were fitted to the $E_{\text{max}}$ model with $R^2 = 0.9648$, $E_{\text{max}} = 89.06$ and $ED_{50} = 0.801$ or (10.8 mins).
The use of 15 tape strips consistently removed an average of 83.37% ± 3.66% (mean ± SD, n = 70) of the SC from the application sites.

NB. Amount removed was not influenced by the time the site was in contact with the formulation.
Bioequivalence of Topical Clotrimazole Formulations: An Improved Tape Stripping Method

Natalie Rae Parfitt, Michael Skinner, Charles Bon, Isadore Kanfer
J Pharm Pharmaceut Sci (www.cspscanada.org) 14(3) 347 - 357, 2011

Small PIVOTAL STUDY

Study population

n = 13 subjects (9 females, 4 males) between the ages of 19 and 30
4 of the 13 subjects were Caucasian, 4 were Black, 1 was of Asian ethnicity and 4 were of Indian or Malay descent.

Study design

• 4 application sites and 1 blank site were delineated on the left arm of each subject
• 2 “test” and 2 “reference” sites were randomized between individuals.
• 90% confidence interval (CI 90%) for the AUC_{test}/AUC_{reference} ratios calculated

• For the untransformed data, the point estimate was calculated by dividing the mean AUC_{test} value by the mean AUC_{reference} value and the CI 90% was determined using Fieller’s/Locke’s method described in the FDA Guidance for topical corticosteroids

• The CV\% associated with the ratios was calculated using the following equation for untransformed data:

\[
CV\% = \sqrt{\frac{MSE}{mean}} * 100
\]
In order to determine the number of subjects required for 80% statistical power the method described for “raw data from a cross over study design” by Chow and Wang* was used.

For the ln-transformed data, the Schuirmann two one-sided test (TOST)** was used to calculate the CI 90% and the point estimate.

The following equation was used to determine the CV% associated with the ratio using ln- transformed data:

\[ CV\% = \sqrt{eMSE - 1} \times 100 \]

## Bioequivalence study on clotrimazole creams

<table>
<thead>
<tr>
<th></th>
<th>Untransformed Data</th>
<th>Transformed Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>$\frac{AUC_{\text{test}}}{AUC_{\text{reference}}}$</td>
<td>0.94</td>
<td>0.97</td>
</tr>
<tr>
<td>CI 90%</td>
<td>0.82 - 1.08</td>
<td>0.82 - 1.13</td>
</tr>
<tr>
<td>Bioequivalence (0.8-1.25)?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CV%</td>
<td>23.62%</td>
<td>23.40%</td>
</tr>
<tr>
<td>Power</td>
<td>n/d</td>
<td>47.24%</td>
</tr>
<tr>
<td>n required for 80% power</td>
<td>19</td>
<td>21</td>
</tr>
</tbody>
</table>
### Effect Of Widening The Bioequivalence Limits

<table>
<thead>
<tr>
<th>Bioequivalence limits</th>
<th>Sample size required for 80 % power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untransformed data</td>
</tr>
<tr>
<td>0.8 – 1.25</td>
<td>19</td>
</tr>
<tr>
<td>0.75 – 1.33</td>
<td>14</td>
</tr>
<tr>
<td>0.7 – 1.43</td>
<td>&lt;13</td>
</tr>
</tbody>
</table>
## Bioequivalence of clotrimazole cream vs clotrimazole gel

<table>
<thead>
<tr>
<th></th>
<th>Transformed</th>
<th>Untransformed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>$\frac{AUC_{test}}{AUC_{reference}}$</td>
<td>1.67</td>
<td>2.06</td>
</tr>
<tr>
<td>CI 90%</td>
<td>0.91 - 3.23</td>
<td>1.06 - 3.99</td>
</tr>
<tr>
<td>Bioequivalence? (0.8 – 1.25)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CV%</td>
<td>27.74 %</td>
<td>24.61 %</td>
</tr>
</tbody>
</table>
Bioequivalence of Topical Clotrimazole Formulations: An Improved Tape Stripping Method
Natalie Rae Parfitt, Michael Skinner, Charles Bon, Isadore Kanfer
J Pharm Pharmaceut Sci (www.cspscanada.org) 14(3) 347 - 357, 2011
• Determination of the bioequivalence of Dermovate creams (0.05% clobetasol propionate) using HSBA and also tape stripping

Objective

• Investigate whether tape stripping can show differences in bioavailability between the same and different topical products, i.e. the capability to measure bioequivalence or bio-inequivalence
• Pivotal TS study - 30 subjects

• Same Dermovate® cream as the test and reference product in the pivotal HSBA study

• Dovate® cream vs Dermovate® cream

• Dermovate® ointment vs Dermovate® cream
### Bioequivalence assessment of identical products
(test –Dermovate® cream, reference – Dermovate® cream)

<table>
<thead>
<tr>
<th></th>
<th>Mean T/R ratio (%)</th>
<th>90% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Locke’s</td>
<td>Log-transformed</td>
</tr>
<tr>
<td>HSBA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromameter</td>
<td>104.3</td>
<td>-</td>
</tr>
<tr>
<td>Visual</td>
<td>102.9</td>
<td>-</td>
</tr>
<tr>
<td>Tape stripping</td>
<td>101.8</td>
<td>101.4</td>
</tr>
</tbody>
</table>

Comparison of Tape Stripping with the Human Skin Blanching Assay for the Bioequivalence Assessment of Topical Clobetasol Propionate Formulations
Wai Ling Au, Michael Skinner, Isadore Kanfer, J Pharm Pharmaceut Sci . 13(1) 11-20, 2010
<table>
<thead>
<tr>
<th>Study Type</th>
<th>T/R ratio (%)</th>
<th>Confidence interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pivotal TS Study (n=30)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dovate® cream vs Dermovate® cream</td>
<td>92.4</td>
<td>80.3 – 106.0</td>
</tr>
<tr>
<td>Dermovate® ointment vs Dermovate® cream</td>
<td>59.1</td>
<td>49.3 – 70.2</td>
</tr>
</tbody>
</table>

- Reference product: Dermovate® cream
- Test products: Dovate® cream and Dermovate® ointment

Comparison of Tape Stripping with the Human Skin Blanching Assay for the Bioequivalence Assessment of Topical Clobetasol Propionate Formulations
Table 2. Pivotal TS studies of clobetasol propionate creams and ointment products using AUC<sub>corr</sub> data and AUC<sub>uncorr</sub> data.

<table>
<thead>
<tr>
<th>Pivotal TS Studies</th>
<th>Mean (%)</th>
<th>T/R ratio (%)</th>
<th>90 % CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untransformed</td>
<td>Log-transformed</td>
<td>Untransformed</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;corr&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dovate® Cream vs. Dermovate® Cream</td>
<td>93.8</td>
<td>92.8</td>
<td>84.7-103.6</td>
</tr>
<tr>
<td>Dermovate® Ointment vs. Dermovate® Cream</td>
<td>66.3</td>
<td>55.2</td>
<td>48.8-82.2</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;uncorr&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dovate® Cream vs. Dermovate® Cream</td>
<td>93.4</td>
<td>93.6</td>
<td>86.3-101.2</td>
</tr>
<tr>
<td>Dermovate® Ointment vs. Dermovate® Cream</td>
<td>95.9</td>
<td>96.3</td>
<td>86.8-106.1</td>
</tr>
</tbody>
</table>
A comparison between the use of the AUCuncorr and AUCcorr values of the different formulations obtained from tape stripping. (a) mean AUCuncorr values with SEM and (b) mean AUCcorr values with SEM of Dovate® cream, Dermovate® ointment and Dermovate® cream for all subjects (n = 30).
Optimization – method to be carried out strictly in accordance with the specified protocol and properly powered for statistical evaluation of BE

- Control sources of variability such as:
  1. Appropriate dose duration
  2. Careful removal of residual application prior to TS
  3. Controlled systematic TS orientation of each site
  4. Normalization of individual skin thickness using TEWL
  5. Control of dose and application thereof
  6. Avoidance of areas of the volar aspect of the forearm where increased variability in uptake may occur such as areas near the wrist and elbows
  7. Effects of temperature and humidity of environment

**Statistical Considerations:** No regulatory guidelines regarding analysis of TS data. The clinical relevance of the currently used 90% CI of BE limits of 0.8 -1.25 is questionable. This was recognized in the draft DPK guidance where the limits were relaxed to 0.70 – 1.43.

Analysis of each skin strip individually and normalizing the amount of SC removed using TEWL provides detailed information regarding the amount and extent of drug penetration. Previous TS studies only the total amount of drug present in the SC was used as the parameter for BE assessment and the distribution of drug throughout the SC was not considered. Our studies showed that CLZ was not uniformly distributed throughout the SC and it is possible that the distribution of drug throughout the SC will affect the efficacy of the product. Therefore by considering AUC of the amount of drug/tape strip vs relative SC depth profile as an indicator of bioavailability using a pre-determined dose duration and correcting for differences in thickness of SC between subjects, this parameter is clearly appropriate to determine BE of such products.
Open Flow Microperfusion (OFM)

Acknowledgement: Dr. Frank Sinner

- allows continuous sampling of interstitial fluid (ISF) in target tissue
- guarantees direct access to the ISF (whether dermal, adipose or muscle tissue)
- samples interstitial fluid (ISF) directly: no limitations regarding size, protein-binding or lipophilicity of API
Working Principle of OFM

OFM probe: perfusate in direct contact with ISF at constant flow rate

Interstitial fluid
Working Principle of OFM
Comparison: OFM vs. MD

OFM: 100 μm open exchange areas

MD: membrane, nm-μm pores
- preclinical use
- clinical use, up to 48h
- mobile subjects
- multiple probes
- multiple sites
- multiple tissues (e.g. dermis/cutis; muscle and adipose tissue)
Wearable pump with active push and pull mode

sampling unit

minimally invasive probes

stabilization ring

multiple sites
IN VITRO OPTION for BIOWAVER

Contains Nonbinding Recommendations

Draft Guidance on Acyclovir

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Acyclovir

Form/Route: Ointment: Topical

Recommended study: 2 Options: In Vitro or In Vivo Study

I. In Vitro option:

To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which "any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence" may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all of the following criteria must be met:

i. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterization of the test and RLD formulations.

iii. Acceptable comparative in vitro drug release rate tests of acyclovir from the test and RLD formulations.
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  R. Tettey-Amlalo-(TS & DMD)
  W-LAu-(HSBA, TS & DMD)
  N.Parfitt-(TS)
- Post-Doctoral Fellow. Dr.S.S.R.Patnala (Pharm.Anal.)
- Research Collaborators:
  Dr.M.Skinner – Biopharmaceutics Research Institute, Rhodes University, South Africa - (Topical Medicines Research Program)
• THANK YOU for your attention.