CHALLENGES WITH CLINICAL ENDPOINTS – BIOEQUIVALENCE

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BACKGROUND

• KELAWER LEGISLATION
  - ENTITLEMENT – EFFICACY

• FDA DERMATOLOGY
  - CORTICOID CLASS LABEL
    - PSORIASIS
    - ATOPIC DERMATITIS
  - DOUBLE BLIND “PLACEBO” CONTROLLED DATA
PHOTOGRAPHY EXAMPLAR – ACNE

COOK METHOD: (ARCH DERM, 115, 571,79)
• OBJECTIVE
• INTRA & INTER GRADES CONSISTENCIES
• VERIFICATION
• TRAINING & VALIDATING GRADERS

(CHIANG: SKIN LESION METRICS – ROLE OF PHOTOGRAPH)
(AGACHE: SKIN METRIC, 2ND Ed, SPRINGER)
PHOTOGRAPHY
GLOBAL ASSESSMENT – MPA

FINASTERIDE (1 mg) vs PLACEBO

Vertex Scalp

Mean Change from Baseline

Men 18-41

PROOF OF CONCEPT

• PAIRED COMPARISON –
  SULZBERGER              WW II

• PRINCIPLE:
  EYES                     GREAT COMPARITOR

• EXAMPLAR:
  SMALL PLAQUE ASSAY       PSORIASIS

• ADVANTAGE:  PERHAPS LESS TOXIC DATA NEEDED

• DISADVANTAGE:  LESS DISCRIMINATING HUMAN TOX INFO
PROOF OF CONCEPT

ARMITAGE DESIGN

A

B

SMALLER GROUPS POSSIBLE
ALOPECIA

HAIR WEIGHT
## PLACEBO

**BENZOYL PEROXIDE TOPICAL**

**PER CENT REDUCTION**

<table>
<thead>
<tr>
<th></th>
<th>ACTIVE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Inflammatory</td>
<td>41%</td>
<td>27% (14 D.)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>34</td>
<td>28 (6)</td>
</tr>
<tr>
<td>Success</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

*(VALUE OF "NO TREATMENT GROUPS)*

(LAMEL, 2012)
<table>
<thead>
<tr>
<th>NAME</th>
<th>REDUCTION BY BRAND (%)</th>
<th>REDUCTION BY VEHICLE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 % TRETINOIN CREAM</td>
<td>39 (143)</td>
<td>20 (139)</td>
</tr>
<tr>
<td>0.1% ADAPALENE CREME</td>
<td>32 (294)</td>
<td>17 (293)</td>
</tr>
<tr>
<td>5% DAPSONE GEL</td>
<td>38 (1,506)</td>
<td>31 (1,504)</td>
</tr>
<tr>
<td>1% CLINDAMYCIN</td>
<td>38 (162)</td>
<td>27 (82)</td>
</tr>
<tr>
<td>0.1% ADAPALENE + 2.5% BP</td>
<td>50 (564)</td>
<td>27 (489)</td>
</tr>
<tr>
<td>1% CLINDAMYCIN + 5% BP</td>
<td>47 (215)</td>
<td>20 (168)</td>
</tr>
<tr>
<td>1% CLINDAMYCIN + 5% BP</td>
<td>54 (397)</td>
<td>19 (177)</td>
</tr>
<tr>
<td>0.0255 TRETINOIN GEL</td>
<td>41 (845)</td>
<td>23 ± 5.0</td>
</tr>
<tr>
<td>MEAN ± SD</td>
<td>42 ± 7.1</td>
<td>23 ± 5.0</td>
</tr>
</tbody>
</table>
PLACEBO RESPONSE

Studies

Odds Ratio [95% CI]

Mease et al., 2000
23.04 [1.26, 420.37]

Chaudhari et al., 2001
15.30 [2.46, 95.19]

Krueger et al., 2002
4.45 [2.50, 7.90]

Lebwohl et al., 2003
2.84 [1.70, 4.76]

Lebwohl et al., 2003
6.47 [2.79, 15.03]

Leonardi et al., 2003
10.74 [4.92, 23.44]

Gottlieb et al., 2003
22.95 [9.83, 179.67]

Gordon et al., 2004
9.56 [4.34, 21.05]

Mease et al., 2004
9.93 [2.88, 34.27]

Gottlieb et al., 2004
63.20 [18.72, 213.41]

Antoni et al., 2005
87.11 [20.26, 374.46]

Leonardi et al., 2005
27.33 [8.53, 87.58]

Antoni et al., 2005
213.00 [12.40, 3657.36]

Papp et al., 2005
22.62 [9.79, 52.25]

Mease et al., 2005
194.55 [46.18, 819.51]

Reich et al., 2005
150.63 [35.96, 630.96]

Papp et al., 2006
10.36 [4.74, 22.66]

Dubertret et al., 2006
10.33 [5.50, 19.43]

Gordon et al., 2006
49.22 [11.25, 215.35]

Krueger et al., 2007
116.20 [15.85, 851.81]

Menter et al., 2008
40.27 [25.09, 64.64]

Leonardi et al., 2008
62.73 [30.30, 129.89]

Papp et al., 2008
63.17 [37.46, 106.52]

Van der Kerkhof et al., 2008
27.00 [3.57, 204.40]

Gottlieb et al., 2009
18.33 [6.07, 55.36]

Kavanaugh et al., 2009
35.19 [10.93, 113.34]

Asahina et al., 2010
44.00 [10.16, 190.56]

Torii et al., 2010
80.65 [4.46, 1458.58]

Gottlieb et al., 2011
21.74 [5.12, 92.37]

Strober et al., 2011
9.04 [3.43, 23.84]

Tsai et al., 2011
38.95 [10.85, 139.83]

Random Effects Model Estimate
23.94 [16.02, 35.76]

Odds Ratio (log scale)
PLACEBO RESPONSE

PSORIASIS BIOLOGICS

OVERALL 4.1%

RANGE 0 – 18 %

NOTE THE 0 PLACEBO EFFECT

(LAMEL: ARCH DERM RES, 304:707)
## Factors determining percutaneous absorption

<table>
<thead>
<tr>
<th>Steps</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1     | Release from vehicle  
- Varies with solubility in vehicle, concentration, and pH, et al. |
| 2     | Kinetics of skin penetration  
- Influenced by anatomical site, degree of occlusion, intrinsic skin condition, animal age, concentration of dosing solution, surface area dosed, frequency of dosing, post absorption, etc. |
| 3     | Excretion kinetics |
| 4     | Tissue disposition |
| 5     | Substantivity to skin |
| 6     | Wash effects  
- Wash resistance; Wash enhancement |
| 7     | Rub effects  
- Rub resistance; Rub enhancement |
| 8     | Transfer – skin, clothing + inanimate surface |
| 9     | Exfoliation |
| 10    | Volatility |
| 11    | Binding – all layers |
| 12    | Anatomic pathways |
| 13    | Lateral spread |
| 14    | Vascular perfusion** |
| 15    | Cutaneous metabolism |
PERCUTANEOUS PENETRATION

INFLUENCE OF SKIN MODEL

IN VITRO PERFORMANCE

(INT J PHARMAC 434: 80)
PERCUTANEOUS PENETRATION

INTERINDIVIDUAL VARIATION

ORAL vs DERMAL

(J PHARM SCI, 101: 4293, 2012)
<table>
<thead>
<tr>
<th>DRUG</th>
<th>FDA APPROVAL YEAR</th>
<th>WITHDRAWAL YEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BITHIONOL</td>
<td>- - -</td>
<td>1967</td>
</tr>
<tr>
<td>DIBROMSALAN</td>
<td>- - -</td>
<td>1975</td>
</tr>
<tr>
<td>METABROMSALAN</td>
<td>- - -</td>
<td>1975</td>
</tr>
<tr>
<td>TRIBOMOSALAN</td>
<td>- - -</td>
<td>1975</td>
</tr>
<tr>
<td>3,3,4,5– TETRACHLOROSALICYLANILIDE</td>
<td>- - -</td>
<td>1975</td>
</tr>
<tr>
<td>CHLOROFORM</td>
<td>- - -</td>
<td>1976</td>
</tr>
<tr>
<td>DRUG</td>
<td>FDA APPROVAL YEAR</td>
<td>WITHDRAWAL YEAR</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>AZARIBINE (TRIAZURE TABLETS)</td>
<td>1975</td>
<td>1977</td>
</tr>
<tr>
<td>ZIRCONIUM AEROSOL</td>
<td>- - -</td>
<td>1977</td>
</tr>
<tr>
<td>POTASSIUM ARSENITE (FOWLER’S SOLUTION)</td>
<td>- - -</td>
<td>1980</td>
</tr>
<tr>
<td>CHLOROHEXIDINE GLUCONATE TOPICAL TINCTURE (HIBITANE)</td>
<td>1978</td>
<td>1984</td>
</tr>
<tr>
<td>TEMAFLOXACIN (OMNIFLOX)</td>
<td>1992</td>
<td>1992</td>
</tr>
<tr>
<td>DRUG</td>
<td>FDA APPROVAL YEAR</td>
<td>WITHDRAWAL YEAR</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>TERFENADINE (SELDANE)</td>
<td>1985</td>
<td>1997</td>
</tr>
<tr>
<td>ASTEMIZOLE (HISMANAL)</td>
<td>1988</td>
<td>1999</td>
</tr>
<tr>
<td>ETRETINATE (TEGISON)</td>
<td>1986</td>
<td>2002</td>
</tr>
<tr>
<td>EFALIZUMAB (RAPTIVA)</td>
<td>2003</td>
<td>2009</td>
</tr>
</tbody>
</table>

“COMPARATIVE EFFECTIVENESS OF NEW MARKETED MEDICATIONS”

& BIOENGINEERING

(CLIN PHARM & THER 90: 777)
COURSES / INSTITUTE

(SPECIALIZED)
EVIDENCE – BASED TRAINING
(INSTITUTIONAL MEMORY – CODIFIED)

• EXPERIMENTAL DESIGN
• GRADING
• “CERTIFICATION”
ROLE OF 21ST CENTURY MEDICINE’S REGULATOR

(M. LUMPKIN: CLIN PHARM THER 92: 486, 2012)
• FDA'S ROLE

• INTERNATIONAL REGULATORS

SEEN ALL (OR ALMNOST ALL) – DATA AND LEARNED
FUNDING

• GOVERNMENT

• INDUSTRY

• “PHILANTHROPY”
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