FDA’s Experience and Concern in the Evaluation of DPK Data

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Disclaimer: The presentation today should not be considered, in whole or in part as being statements of policy or recommendation by the US Food and Drug Administration.
Outline

• DPK and New Drug Development
  – How Did We Get Here?
  – Where Are We?
  – Where Are We Going?
“Standard” Development Paradigm
Prior to the early 1990s, most topical dermatologicals had little or no direct assessment of in vivo bioavailability.

Clinical efficacy trials or surrogate markers of drug absorption were used.

Waivers of in vivo bioavailability testing were the norm and not the exception.
Dermal Drug Review
“Paleoregulatory”

- Clinical Trials
  - Direct assessment of clinical utility
  - Relatively long duration to see maximal benefit in patients

- Surrogate Markers
  - Often provide an assessment not of efficacy but of safety (i.e. HPA Axis suppression)
  - Often no correlation between marker (vasoconstriction) and therapeutic benefit
Bioavailability

21 CFR § 320.1 Definitions.

(a) Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.
The Riddle of “Effect Site” Concentrations for a Topically Acting Drug

Stratum Corneum

Peripheral Compartment

Central Compartment

Effect Site

Topical Application

?
Determinants of Topical Bioavailability

It is the complex interaction of drug substance, formulation-dosage form, and those skin factors that affect the barrier function of the skin that determines systemic drug availability, its profile over time, and product design selection.
Types of Evidence to Establish Bioavailability or Bioequivalence*

- Determine the drug/metabolite levels in man in biological fluids as a function of time
  - An in vitro test that has been correlated with and is predictive of in vivo bioavailability
  - An in vivo test in animals
- Urinary excretion data
- In vivo test of an acute pharmacological event over time
- Well controlled clinical trials
- In vitro testing

*21 CFR 320.24
Where is DPK?
A Statement of Fact

• Since Bio-International 2008 the FDA has not approved a single topical application using these methods for a new drug!
The Sponsor’s Role in Innovation

- Since Bio-International 2008 less than 5 sponsors have proposed or submitted IND data using microdialysis
- Since Bio-International 2008 no sponsor have proposed or submitted IND data using IR or other spectroscopic techniques
- Since Bio-International 2008 no sponsor have proposed or submitted IND data using DPK
"The fault, dear Brutus, is not in our stars,
But in ourselves, that we are underlings."

Cassius

Julius Caesar (I, ii, 140-141)
Cascade of Knowledge

- Theoretical Basis
- Laboratory Use in Animals
- Experimental Use in Humans
- Clinical Use in Humans
- Regulatory Use in Drug Development
- Pre-Clinical Use
- Clinical Use
General Test Characteristics

- Well defined procedures
  - Validation
  - Standardized Training
- Be reproducible
  - Run to Run
  - Site to Site
- Be predictable
- Be relevant clinically
DPK and Clinical Relevance

• For New Drugs, in vivo BA testing is focused “primarily” on supporting safety, ie. assessing in vivo systemic bioavailability
• DPK is not really feasible in most (if not all) dermatologic diseases
• Normal skin is a very poor predictor of diseased skin absorption
DPK and Reproducibility

• Tape is tape is tape?
  – Cannot, at this time, assure that the tape used at one site is the same at another
    • Adhesives age
    • Tape manufacturers can change adhesive systems at any time without announcement
  – The lack of assurance of “tape equivalence” from one batch, year, manufacturer, is a major weakness in terms of reproducibility
    • What would “tape assurance” look like?
Quo Vadis?

- Are alternative assessment methods DOA at the FDA?
- Will the FDA give innovative ideas a hearing?
The FDA’s “DUAL” Role

Regulations

Conservative

Science

Innovation

FDA
Bringing Clinical Pharmacology Tools to Bear

INNOVATIVE ANALYSES
• Improved Computing Resources
• Quantitative drug-disease-trial models
• Exposure-response models

INNOVATIVE TRIAL DESIGNS
• Clinical trial simulations
• Enrichment, adaptive, dose-response

KNOWLEDGE MANAGEMENT
• Leverage prior data
Innovative Analyses

- Exposure-response to support benefit/risk and dose selection
- Disease-drug-trial models to gain insights into biomarkers and endpoints
- Prioritize drug interactions studies based on in vitro and in silico predictions (PBPK)
- PopPK approaches for intrinsic/extrinsic factors

DEVELOPMENT IMPACT
- Streamline Clin-Pharm package
- More efficient trials based on mechanistic reasoning

REGULATORY PATHWAY
- Guidance documents
- Critical Path modeling consortia
Willingness to Accept “Non-Traditional” or Innovative Trial Designs

CSL Behring's Corifact Clears FDA On 14-Patient Trial

FDA is reaffirming its willingness to clear drugs for orphan conditions on very unusual data sets with its approval of CSL Behring's Corifact for prevention of bleeding in people with congenital Factor XIII deficiency.
Willingness to Accept “Non-Traditional” or Innovative Trial Designs
Innovation

Stagnation

Challenge and Opportunity on the Critical Path to New Medical Products

FDA Whitepaper on Critical Path issued on March 16th, 2004

http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html
The Unmet Need

- Learning from experience, acceptance of new regulatory tools will be dependent upon the correlation of the obtained results with clinical response.

Validation will be the key to acceptance.
Conclusions

- As new dermal absorption tools are developed and gain acceptance, regulatory policy will have to evolve to maintain its relevancy.

- For NEW DRUGS, Clinical Pharmacology studies currently are generally considered to be safety related trials for topical products.
Conclusions

- At the present time the use of in vivo bioavailability trials as an assessment of topical efficacy is not possible as assessments at the site of action (i.e. the stratum corneum) have not been validated.

- That being said, the FDA is willing to discuss plans and protocols with sponsors or researchers.
A Final Word: Toolkit Development

Translational research, either for Topical drug development or any drug development program, is a partnership between the researcher, the clinician and the regulator.

The mantra often heard in Clinical Pharmacology is:
Right Drug
  Right Dose
    Right Patient
      Right Time

For developers it should be:
Right Tool
  Right Model
    Right Collaboration
      Right NOW!
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