Regulatory Approaches for New Drugs: BA/BE of Topical Drug Products

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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

- Bioavailability and 505(b)(1), (b)(2), (j)
- The Maximal Use Trial
- Trends in Drug Development-The Good & The Bad
- A Perspective on Tools Relative to Clinical Pharmacology
- A Call to Action

Why do we care about in vivo bioavailabilty as it relates to efficacy and safety?

505(b)(1) vs 505(b)(2) vs 505 (J)

- 505(b)(1)-Classical New Drug
- 505(b)(2)-New Formulation/Form, etc.
- 505(j)-Generic Drug Applications

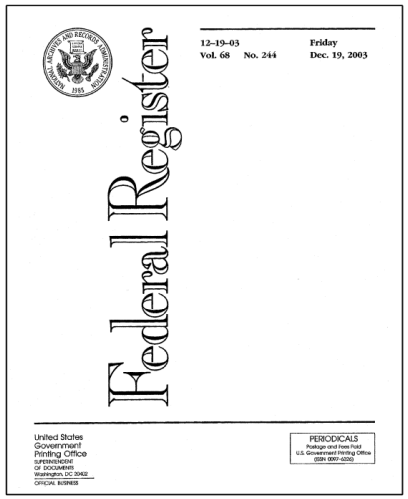
Informational Needs

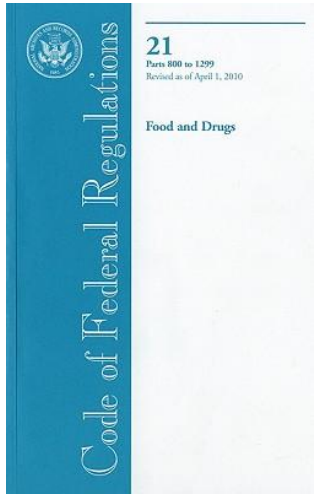
- Each type of application has an inherently different informational need in relation to safety and efficacy.

- In general, bioavailability data can be used to complement the safety and/or efficacy data depending on the drug and indication.

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*.





505(b)(1)

- The classic "NEW DRUG"
- Application consists of studies of both the safety and efficacy of the drug in both animals and humans.
- Bioavailability studies for topical products are primarily safety related studies. They provide a linkage to animal safety data and to dose finding and formulation optimization in humans.
  - A combination of classical pharmacokinetics with clinical pharmacology.

505(b)(1)

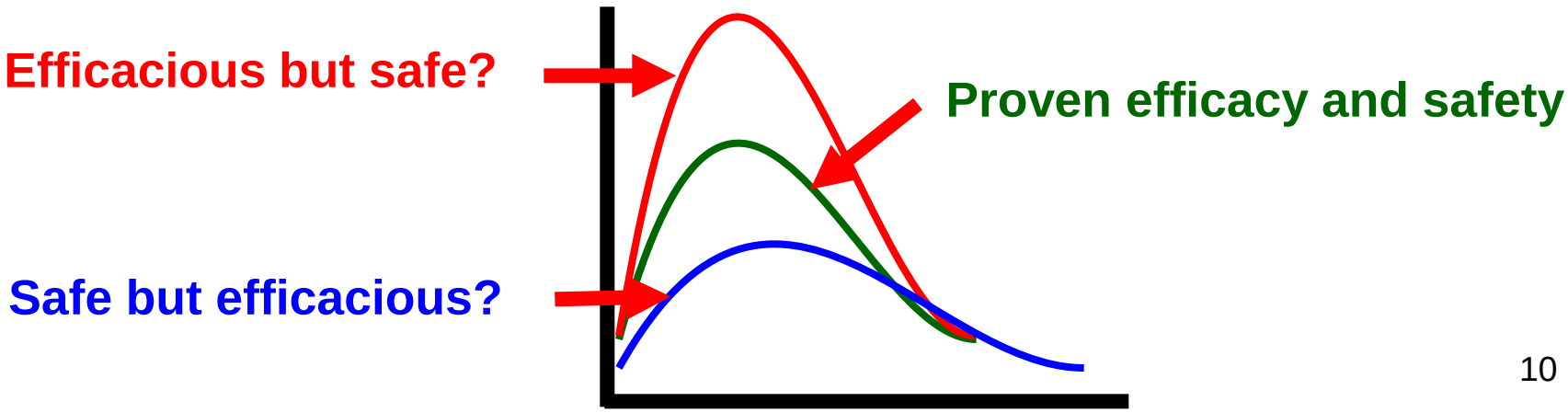
- For topical products, unless another validated test is available, the FDA currently recommends that a "maximal use" study be done in the patient population of interest.
  - The study must represent the largest anticipated usage that is consistent with the clinical trials and anticipated indication/labeling.

505(b)(2)

- New Dosage Form/New Indication/New Patient Population
- These applications build on information from previous approvals for which the applicant does not have a "right of reference"
- Imposes a lesser regulatory burden than a 505(b)(1)

505(b)(2)

- Bioavailability testing is linked to both assessments of safety and efficacy (for systemic treatments).
- For topical products where absorption is not desired, bioavailability testing is primarily a safety assessment

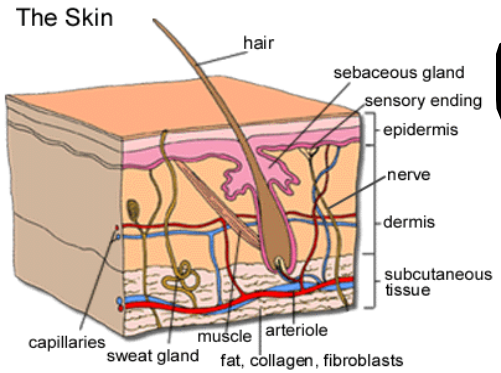


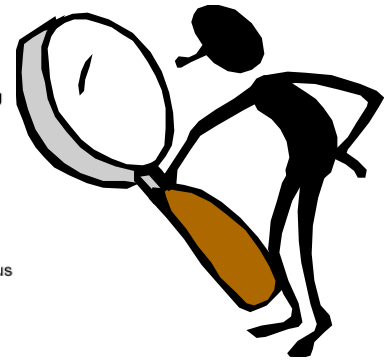
505(j)-

- These are "Generic Drugs" and represent a growing part of the pharmaceutical market as more and more drugs come off patent.
- Traditional in vivo bioequivalence testing has been the cornerstone of approval, with a single dose PK trial in normal volunteers being the "gold standard".
- Other speakers at this meeting have spoken on this topic and I defer to their expertise

Dermal Drug Absorption

- It has been the lack of an ability to assess local drug concentrations and a lack of correlation between systemic levels and local therapeutic effect that has required, to date, the use of clinical trials to assess bioavailability.





http://www.nku.edu/~dempseyd/SKIN.htm

The Maximal Use Trial

- In the mid 1990s the FDA developed and implemented the use of the "maximal use" trial as part of an in vivo bioavailability program.
  - Outgrowth of the dissatisfaction with previous bioavailability assessments
  - Made possible by the refinement of analytical methodologies

Maximum Use Trial "Standard Language"

It has been the Agency's policy to request that a maximal usage trial be undertaken in a suitable number of subjects with the dermatological disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. Such a trial would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

a) Frequency of dosing
b) Duration of dosing
c) Use of highest proposed strength
d) Total involved surface area to be treated at one time
e) Amount applied per square centimeter
f) Method of application/site preparation

The trial itself could be a stand alone trial in phase II or could be a sub-group of subjects in a larger phase III trial. Either approach is acceptable and has been used successfully by other sponsors

Why these elements?

a) Frequency of dosing

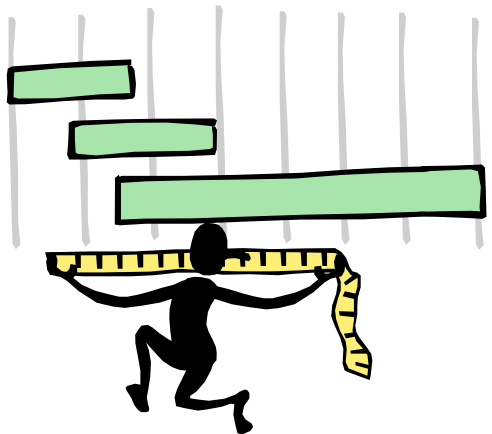
-Prior to this time, NDAs were being submitted for chronic application with only single exposure PK.

-While for oral drug products single doses are considered the most sensitive for BA/BE evaluations, for topical products they are of limited utility from a regulatory perspective

Why these elements?

b) Duration of dosing

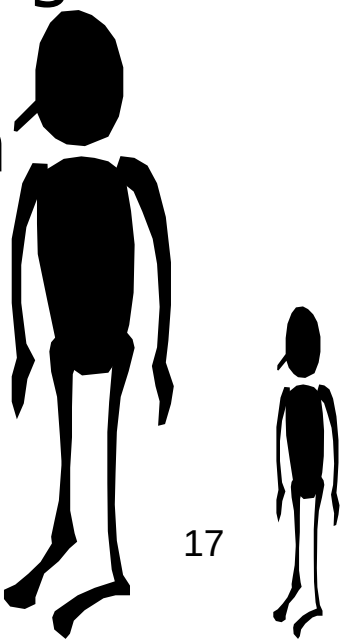
-Like oral controlled release products the duration of the study must be long enough such that the levels detected in the plasma (if any) are the maximal levels possible to inform safety.



Why these elements?

c) Use of highest proposed strength

-Often topical products are developed in a range of strengths. Prior to this time sponsors tended to use the lowest concentration, thus minimizing the potential for absorption while maximizing the safety multiple from animal studies.



Why these elements?

d) Total involved surface area to be treated at one time

-From a practical sense topical application for all but sunscreens is usually limited in adults to <30% of BSA. Even so NDAs were being submitted for indications such as moderate to severe psoriasis with only 5-10% BSA involvement.

$$\text{BSA } (\text{m}^2) = \sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600 \text{ (cm kg/m}^4\text{)}}}$$

Why these elements?

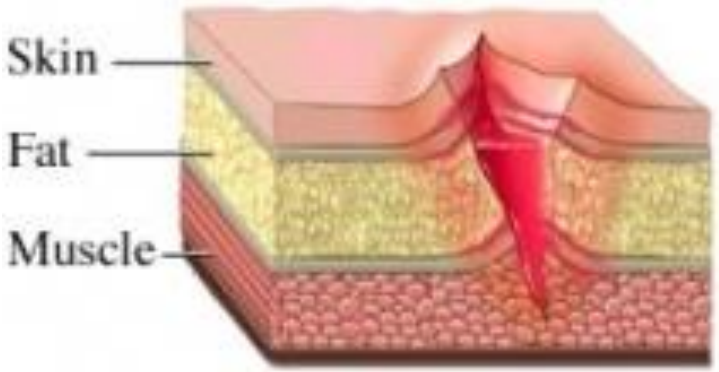
e) Amount applied per square centimeter

-To maximize the amount that can be absorbed one must test the maximum amount expected to be applied by the patient. One cannot expect that all subjects will interpret usage instructions in a similar manner (i.e. “a palm sized amount”.)

Why these elements?

f) Method of application/site preparation

-Related to both the use of soaps and washes but also to debridement in some instances as in wound care or diabetic foot ulcer



The Maximal Usage Trial

- Designed to evaluate the potential for systemic drug absorption at the upper limit of use covered by the clinical trials and allowed for in the label in the patient population of interest.
- While it has been successful in developing better assessments of systemic exposure and safety issues, it is still limited in its ability to assess bioavailability, per se.

The Maximal Usage Trial

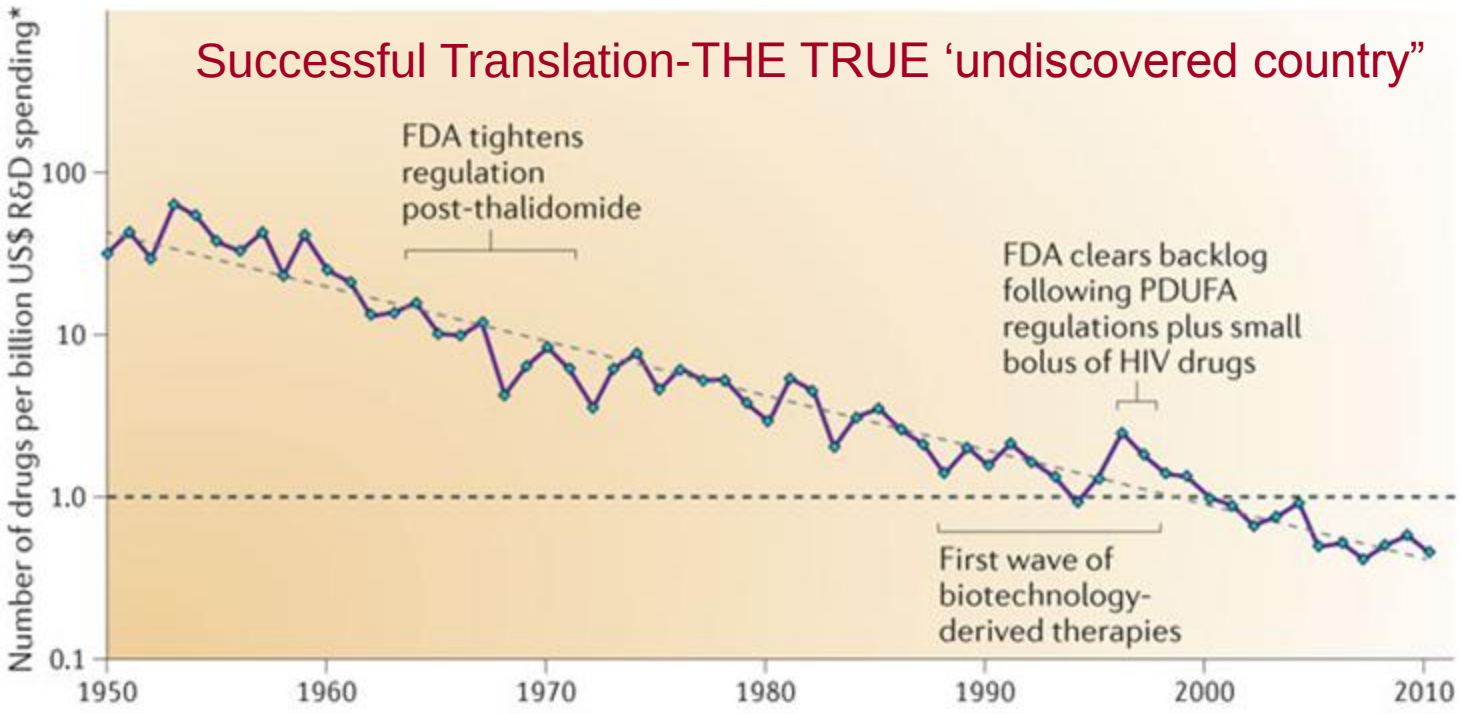
- Limited in that it does have a "1 approach fits all" connotation
  - Even so it does address the earlier shortcomings of dermatologic research
- Does NOT represent the end of FDA thought on dermal drug development.
  - Technology evolves
  - New Methods and New Sciences (nanotechnology)
  - FDA's methods will have to evolve as well
    - The FDA cannot do it alone-nor does it want to

Law of the Instrument

"Give a small boy a hammer,
and he will find that
everything he encounters
needs pounding."

In "The Conduct of Inquiry: Methodology for Behavioral Science"
By Abraham Kaplan

Trends in Drug Discovery



Scannell, JW, et al "Diagnosing the decline in pharmaceutical R&D efficiency"
Nature Reviews Drug Discovery, 11:191-200 (March 2012)

Reasons for lack of success in drug discovery (CNS)

- Lack of fundamental knowledge regarding the causes of CNS disorders
- Absence of biomarkers for diagnosing and monitoring these conditions
- A paucity of animal models that are congruent with the human disease state
- The likelihood that CNS conditions are multifactorial in their etiology

These factors are true for most therapeutic areas.

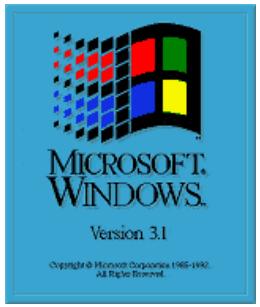
Williams, Michael & Enna, S J "Prospects for neurodegenerative and psychiatric disorder drug discovery" *Expert Opin. Drug Discov. (2011) 6(5):457-463*

Technological Evolution

- As technology evolves, both scientific and regulatory thought must evolve as well to keep pace.
- Every technique we apply to determining true dermal bioavailability has flaws
  - IR/Raman spectroscopy
  - Microdialysis
  - DPK

Drug Development and Computing

- PDUFA-I came into force in 1992
- State of Computers in 1992?
  - Internet Society formed
  - John Scully first uses the term PDA at CES while describing the Apple Newton
  - NSFNET upgraded to T-3 backbone
  - Microsoft introduces Windows 3.1
  - Intel releases the 486DX2 chip (*50 mHz*)
  - Gopher tool Veronica is first released
  - IBM introduces ThinkPad, the industry's first notebook with a 10.4 inch color TFT display.



http://www.computerhope.com

Innovative Analysis-Computing 2013

- In 2013, while paper NDA submissions are still submitted, more and more data comes to the FDA in an electronic format for review.
- The FDA has continued to upgrade its computer resources including the Computational Science Center whose mission is
  - *To support CDER in continually improving the optimal drug evaluation and review process for the entire drug lifecycle while addressing the dynamic nature of the healthcare system*

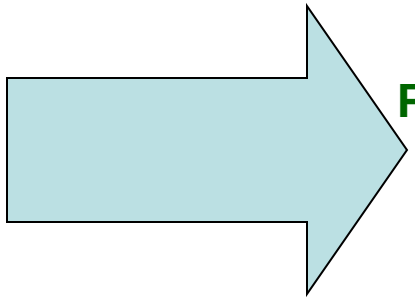
CDER Computational Science Center

Center for Drug Evaluation and Research
CSC
Computational Science Center

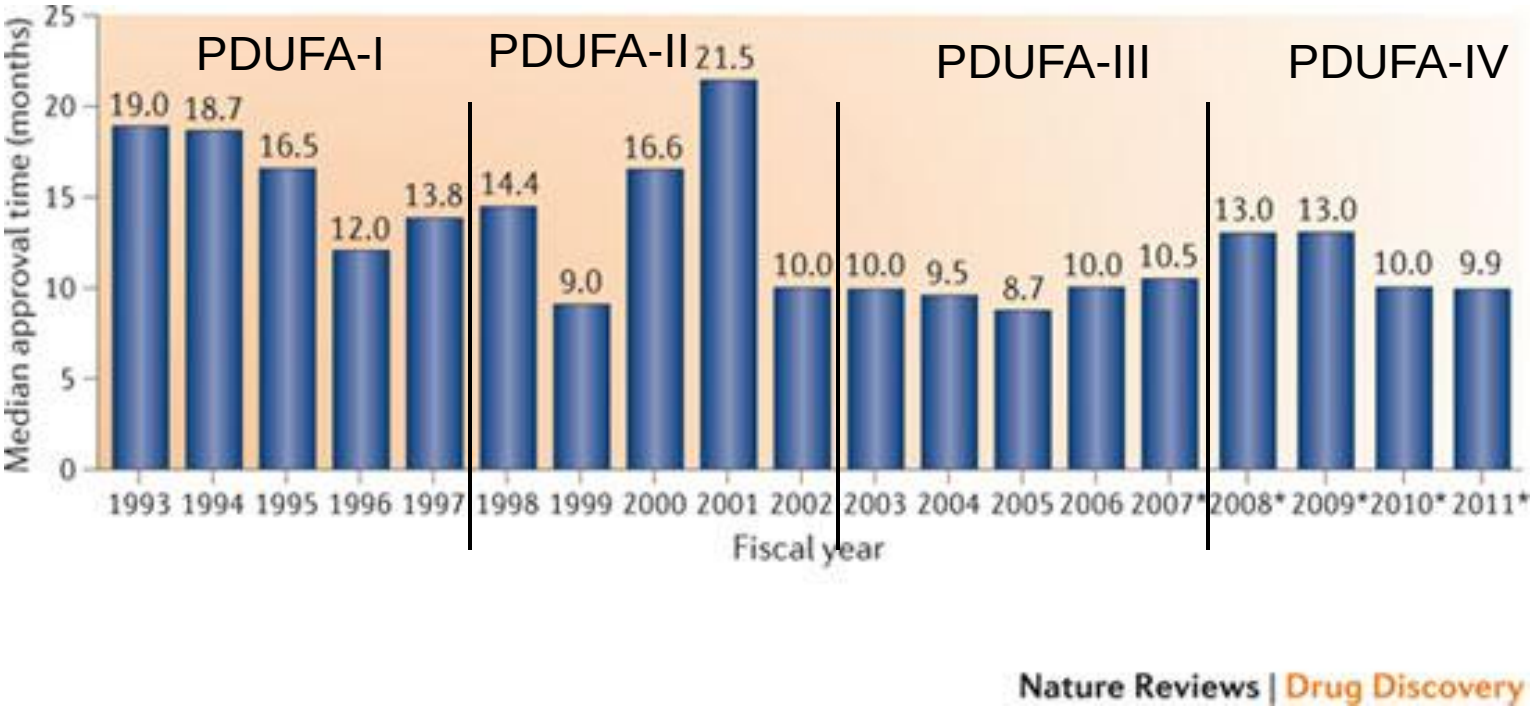
Better Data, Better Tools, Better Decisions

PDUFA and FDA Collaboration

- Embodied in all iterations of PDUFA has been increased communication with the FDA.
  - Type "A" meeting
  - End of Phase 2 meetings
- Beyond PDUFA the FDA has as part of its internal organization given support to the "RESEARCH" portion of the Center for Drug Evaluation and Research
  - Critical Path Projects
  - Regulatory Science Research
  - ORISE Fellows
  - Commissioner's Fellows
  - Office of Women's Health Research Grants



Median Approval Times Under PDUFA



*some applications still pending

Mullard, A, "PDUFA V goes back to basics" Nature Reviews Drug Discovery 11, 586-588 (August 2012)

http://www.circare.org/info5.htm

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

FDA's Critical Path Initiative: Activities

- Bring focus to the need to upgrade infrastructure.
- Trigger public and private critical path research.
- Collaborations and partnerships. Expertise and information needed is spread across disciplines and organizations.
- FDA leadership in collaborative development of appropriate scientific standards can reduce uncertainty in product development planning.

Quo Vadis?

Conclusions

- As new Clinical Pharmacology tools are developed and gain acceptance, regulatory policy will have to evolve to maintain its relevancy.
- For topical products, Clinical Pharmacology trials are generally considered to be safety trials.

Conclusions

- At the present time the direct measurement of in vivo bioavailability "at the site of action" is not possible from a routine regulatory perspective as assessments at the site of action (ie. the stratum corneum) have not been validated.
- The Future is NOW!

Conclusions

- The development and regulatory acceptance of new research methodologies will require academic, clinical, industry and government partnerships.
- Clinical Pharmacologists are uniquely qualified to participate and lead in this area and opportunities should be taken to pursue rational approaches to drug development in a collaborative manner.

Acknowledgements

- The members of my Division
- The support of my friends and co-workers.