The Pursuit of Alternative Methodologies For Demonstrating Bioequivalence for Generic Topical Dermatologic Drug Products

DPK, Q3, Cakes and 2 Pis

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FDA

Magnitude of the Issue

- Most dermatologic diseases are common, chronic and costly (3 C's)
- Topical dermatologic products are often the mainstay of control
- Generic topical dermatologic drug products may lower costs and increase availability to patients

Historical Difficulties

- Demonstration of bioequivalence to Reference Listed Drug (RLD) generally requires clinical trials(s) [320.24 (b) (4)]
- Clinical reports of lesser effectiveness
- Noticeable difference in vehicle properties
- Bad press

Noticeable Difference in Vehicle Properties

- Traditionally focus has been limited to

  Q_1 - qualitative sameness

  and

  Q_2 - quantitative sameness

- Vehicle properties, including drug delivery, also depend on

  "Q_3" - structural (phasic) sameness

Q_3 Sameness and the Law of Duncan Hines and Wilkin

Physical structure of topical dermatologic drug products matters.

314.94 (a) (9) (v)

Inactive ingredients for topical products may not be the same as for the RLD.

Q_1 and Q_2 are not essential.

Manufacturing Process

- Propriety information not available to generic manufacture.
- Even when Q_1 and Q_2 are identical, the product may have very different physical properties, e.g., viscosity, which may affect product performance.

The Question:

How to ensure that information for approval of a generic topical dermatologic product is necessary and sufficient to establish that it is equivalent to the reference listed drug is a problem of regulatory science related to Regulatory Elegance.

“Elegance” in the Sense of

– The synthesis of an organic chemical in the fewest steps with the highest yield

– The mathematical proof with the fewest assumptions and the fewest logical steps

Regulatory Elegance

- Is the identification of the simplest information structure required for a regulatory decision.
- Is not the absence of “regulatory creep” ; it is the opposite.
- Demands focus on the 3 R’s

The 3 R's of Regulatory Elegance

- Reduction - number or extensiveness of required test
- Refinement - optimization of test design for maximum information at minimum cost
- Replacement - substitution of a simpler, cheaper, more informative test

Possible Information Structures for Generic Topical Dermatological Drug Products

- Short term - Reduction and Refinement

  Average scalar (nonquantal) outcomes per patient over several time points to reduce intrasubject variability (increasing power and decreasing number of subjects)

- Long term- Replacement

  Develop alternative methods to assess Q_3 sameness and bioequivalence.

Alternative Methods for Bioequivalence of Topical Dermatological Drug Products

Substantiation of performance parameters [211.194 (a) and USP (1225)]

1. accuracy
2. precision
3. specificity
4. limit of detection
5. limit of quantitation
6. linearity
7. range
8. ruggedness
9. robustness

Validation of Utility

1. intralaboratory reproducibility
2. interlaboratory reproducibility
3. demonstration of replaceability

“Controlled Artifact” Stage

- Substantiation of performance parameters
- Reproducibility both intralaboratory and interlaboratory
- Awaiting the essential final validation step: demonstration of replaceability

The Case Against Using DPK Now to Document BA/BE for Topical Drug Products

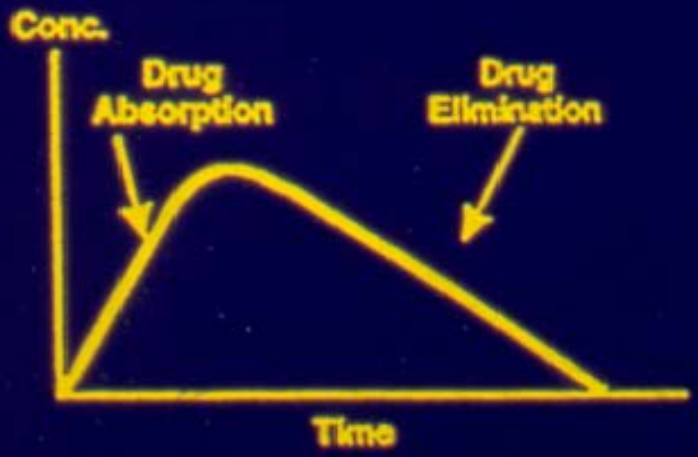
Assumption:

DPK may become reproducible at different laboratories

(a controlled artifact)

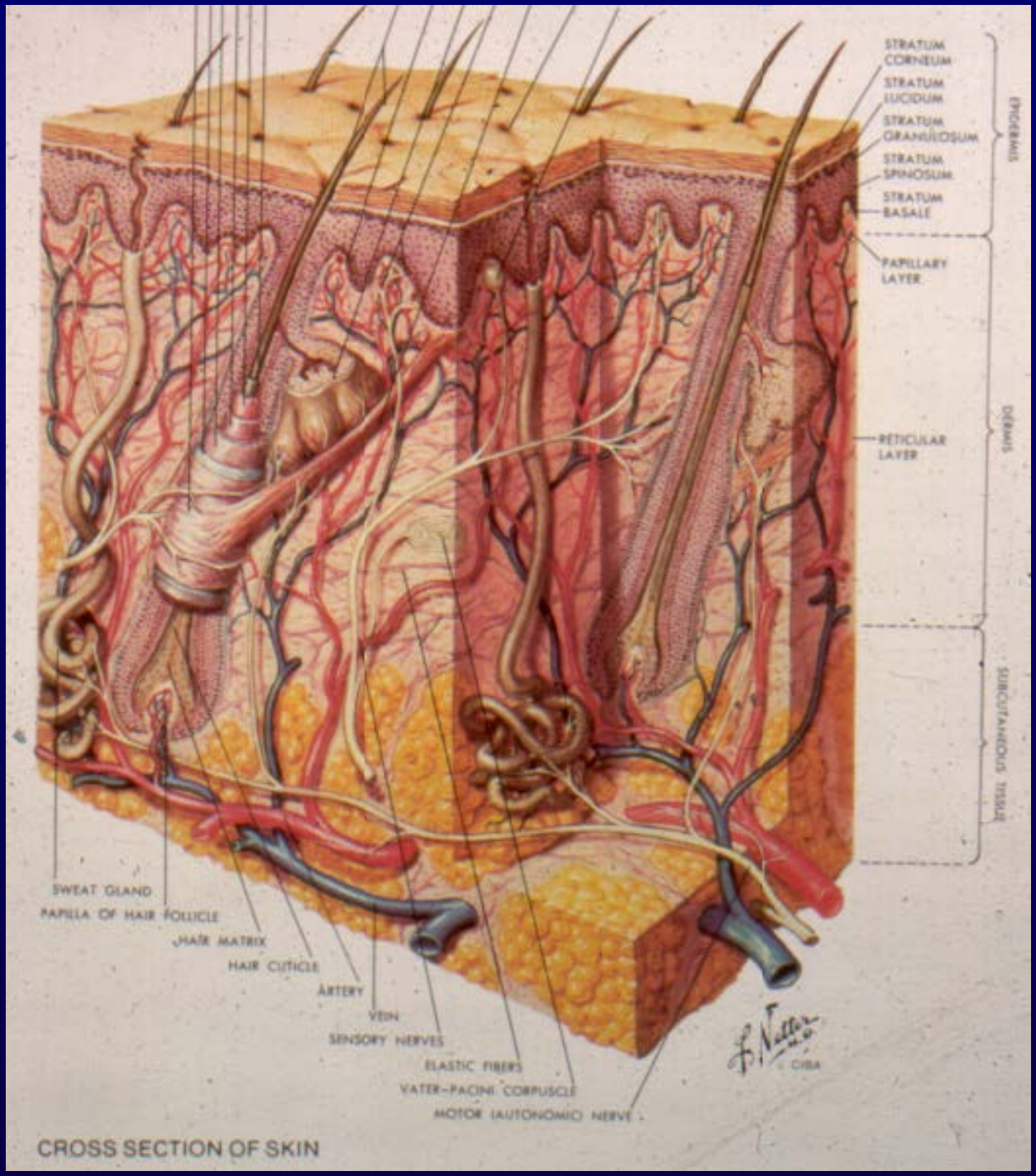
Dermatopharmacokinetic studies

- What Is Dermatopharmacokinetic?
  - Kinetics of the drug in the skin
    Pharmacokinetics applied to skin.



Plasma concentration vs. Time Profile

Skin concentration vs. Time Profile


STRATUM CORNEUM
STRATUM LUCIDUM
STRATUM GRANULOSUM
STRATUM SPINOSUM
STRATUM BASALE
EPIDERMIS
PAPILLARY LAYER
RETICULAR LAYER
DERMIS
SUBCUTANEOUS TISSUE
SWEAT GLAND
PAPILLA OF HAIR FOLLICLE
HAIR MATRIX
HAIR CUTICLE
ARTERY
VEIN
SENSORY NERVES
ELASTIC FIBERS
VATER-PACINI CORPUSCLE
MOTOR (AUTONOMIC) NERVE
F. Netter M.D.
CIBA
CROSS SECTION OF SKIN

Dermatopharmacokinetics

"Dermato-" = skin

Stratum-corneum-pharmacokinetics

Stracorneopharmacokinetics

Stracopharmacokinetics

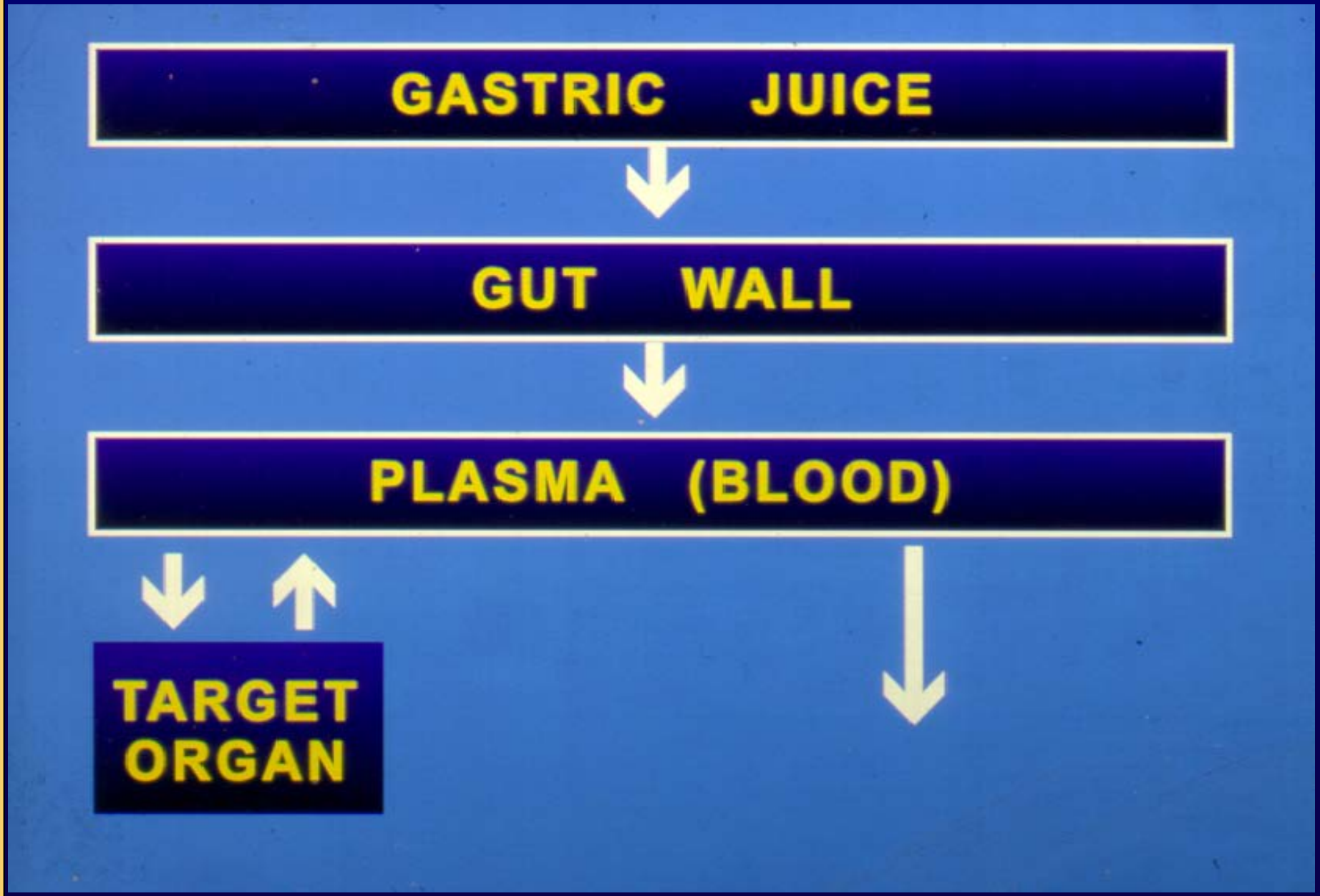
Scpharmacokinetics

"SCPK"

Is the DPK AUC of topical dosage forms analogous to the plasma AUC of oral dosage forms?

Major Problems with the Grand Analogy

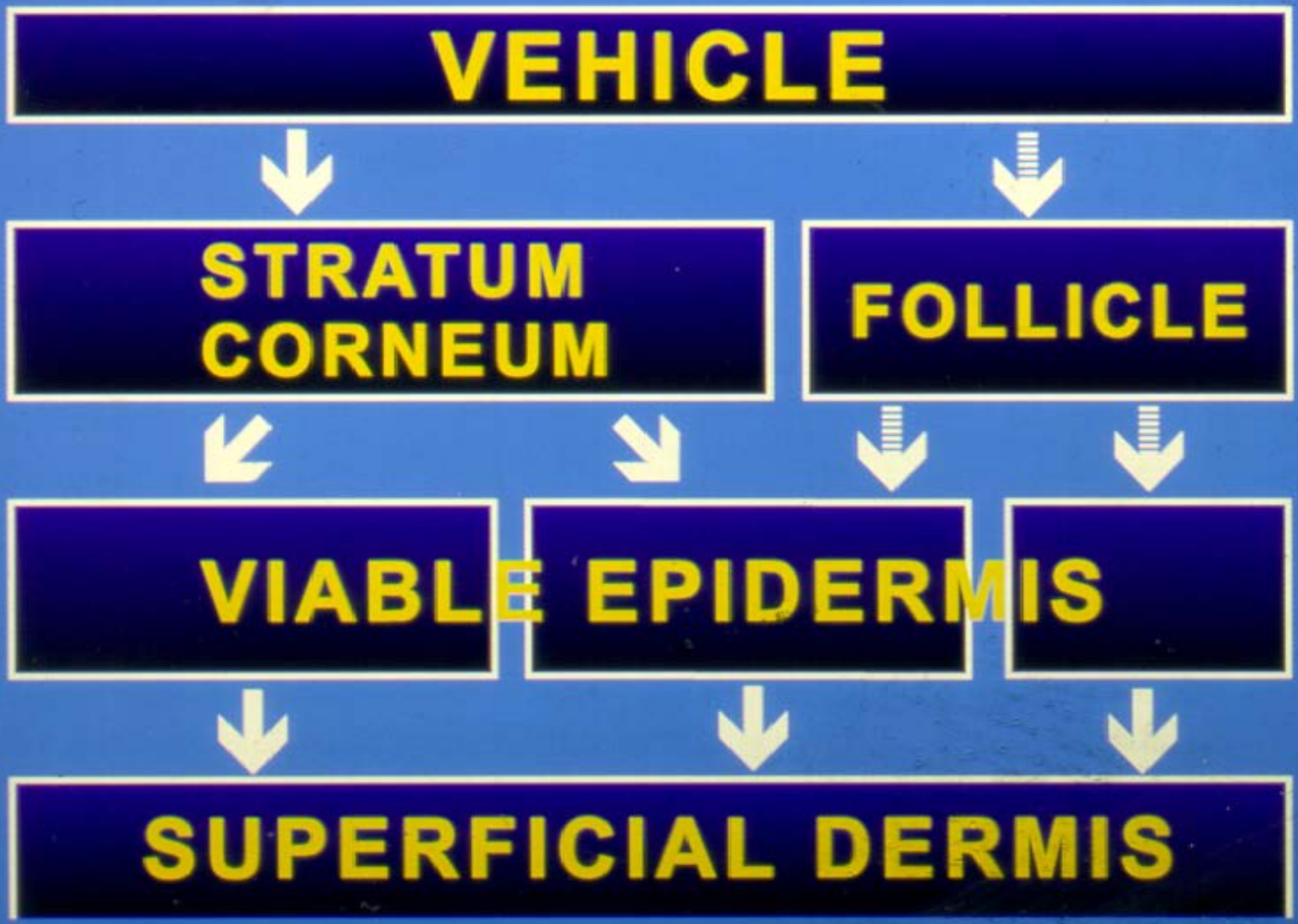
1. Stratum corneum ≠ skin
2. Ignores follicular shunt
   (SC is not sole pathway)
3. SC is not a real compartment
   a. Not well-mixed
   b. No equilibrium with actual target
4. "Healthy SC" is absent in
   a. Diseased skin
   b. Lip
   c. Vaginal mucosa


GASTRIC JUICE
GUT WALL
PLASMA (BLOOD)
TARGET ORGAN

Equilibrium

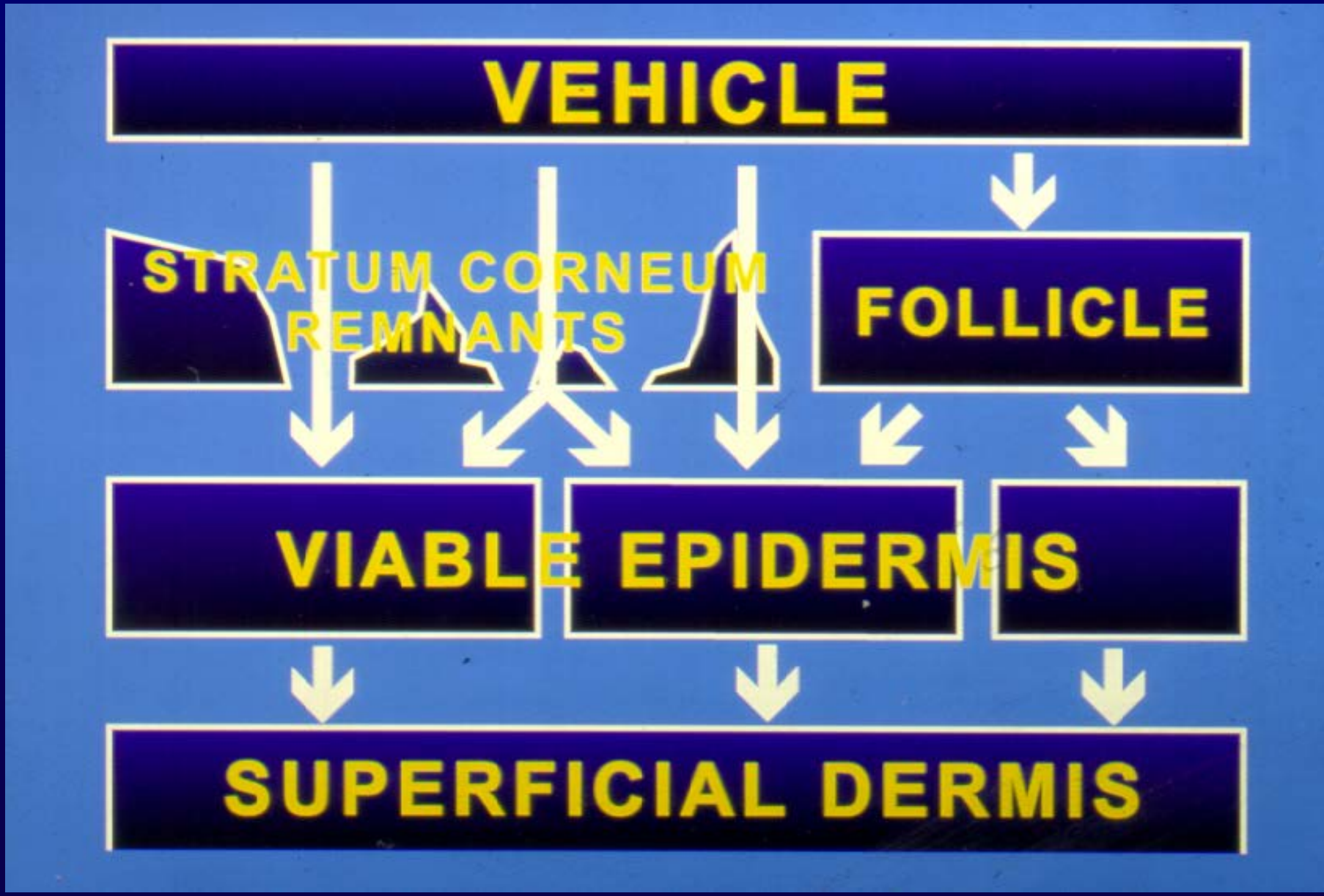
"Plasma levels produced by two generic formulations should be similar at equilibrium, as their plasma level/tissue level ratio will remain constant at equilibrium."

Jamoulle & Schaefer, 1993


VEHICLE
STRATUM CORNEUM
FOLLICLE
VIABLE EPIDERMIS
SUPERFICIAL DERMIS

Healthy SC?

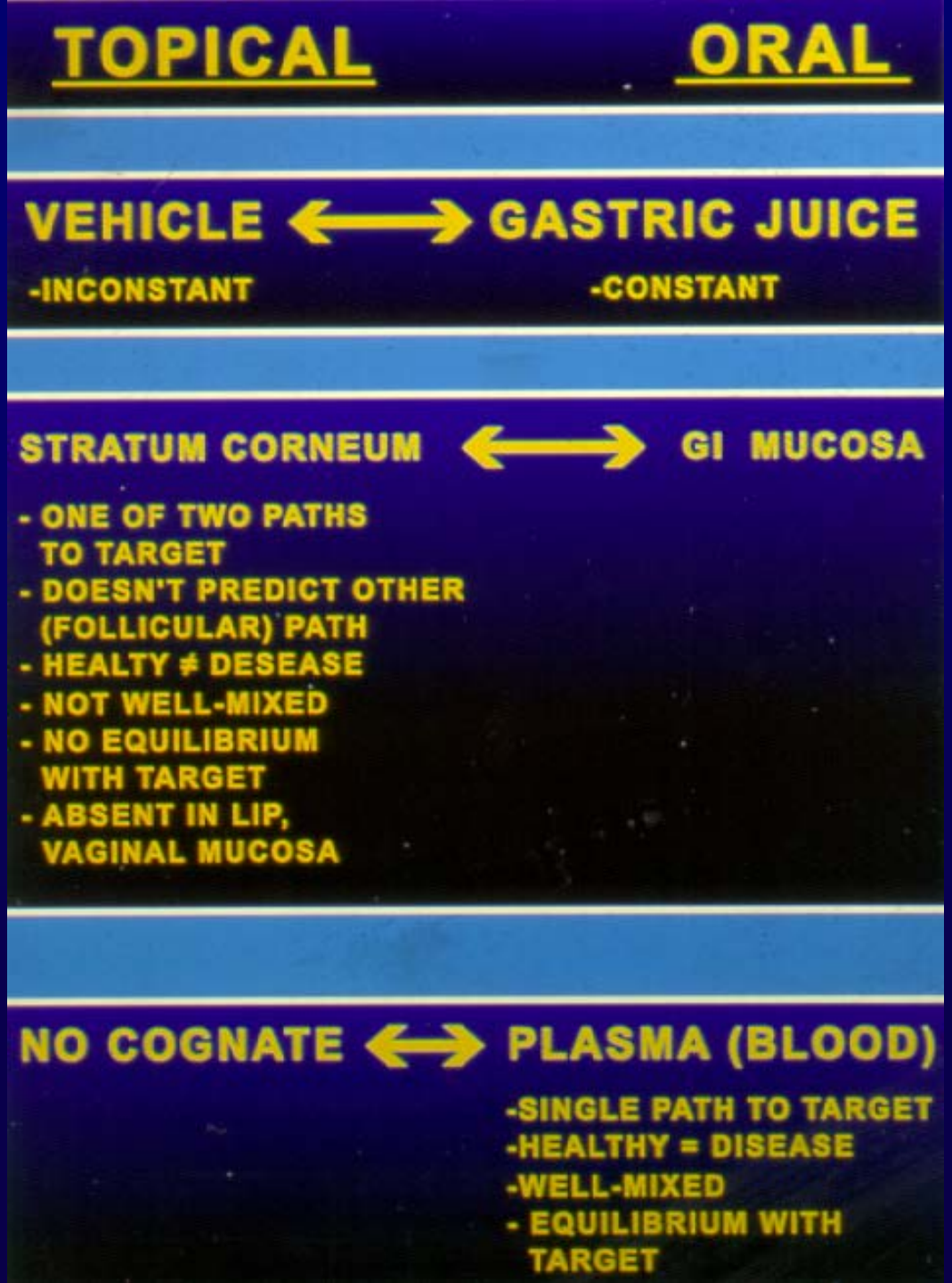
Functionally and anatomically intact SC does not occur in most skin disease, lip, and vaginal mucosa


VEHICLE
STRATUM CORNEUM REMNANTS
FOLLICLE
VIABLE EPIDERMIS
SUPERFICIAL DERMIS

Diseased Skin

"When a dermatological drug is used, it is usually applied to diseased skin, which may not have the same permeability as healthy skin…To simulate diseased skin, the stratum corneum can be removed…"

Jamoulle & Schaefer, 1993


TOPICAL
ORAL
VEHICLE ⟷ GASTRIC JUICE
-INCONSTANT
-CONSTANT
STRATUM CORNEUM ⟷ GI MUCOSA
- ONE OF TWO PATHS TO TARGET
- DOESN'T PREDICT OTHER (FOLLICULAR) PATH
- HEALTY ≠ DESEASE
- NOT WELL-MIXED
- NO EQUILIBRIUM WITH TARGET
- ABSENT IN LIP, VAGINAL MUCOSA
NO COGNATE ⟷ PLASMA (BLOOD)
-SINGLE PATH TO TARGET
-HEALTHY = DISEASE
-WELL-MIXED
- EQUILIBRIUM WITH TARGET

Repeated Dosing

"The metabolic activity and permeability of the skin may be changed under the effect of repeated exposure to the product during a toxicity or clinical study."

Jamoulle & Schaefer, 1993

AAPS/FDA Workshop Report:

Bioequivalence of Topical Dermatological Dosage Forms: Methods of Evaluation of Bioequivalence

Pharmaceutical Res 1998; 15: 167-71

"Before a DPK method is adopted as a basis for BE, it must be shown that differences in DPK capture or reflect significant clinical(ly) important differences in formulations."

Hoosier Pi

House Bill No. 246, Indiana State Legislature, 1897

Edwin J. Goodman, M.D.

House Committee on Swamp Lands

House Committee on Education

House voted 67 – 0 on February 5, 1897

Prof. C.A. Waldo, Purdue Professor

Senate debated February 12, 1897 and postponed further consideration

Ancient Egyptian Pi

By geometric construction:
Golden Mean, φ

$$4\sqrt{\phi} = 3.1446056$$
$$\pi = 3.1415926$$

Sufficient exactitude for the building materials and architecture of Ancient Egypt through the Middle Ages (VALIDATION)

Validation: Peer-Reviewed Demonstration of Replaceability

1. Does method make biological sense? (e.g., Does the method use healthy skin with an intact stratum corneum barrier for products intended for diseased skin without an intact stratum corneum barrier?

Validation (continued)

2. Can the method reproducibly demonstrate 1)equivalence between the RLD and a clinically demonstrated bioequivalent product and 2)superiority (or inferiority) to a clinically - demonstrated superior (or inferior) bioinequivalent product in an adequate, well-controlled, and blinded comparative study with at least three arms: RLD, clinically bioequivalent product, and clinically bioinequivalent product?

Conclusions

1. There is a compelling public health need for good quality generic topical dermatological drug products.

2. In the short term, reduction and refinement of clinical trial designs may decrease development costs and provide sufficient evidence.

Conclusions

3. In the long term, replacement of clinical trials by alternative methodologies supplemented by the demonstration of sameness in physical properties may decrease development time and costs even further, providing the greatest regulatory elegance.