Implications of skin anatomy, skin (patho-) physiology, and product physico-chemistry on FDA regulatory approach for generic dermatologic products

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Perspectives in Percutaneous Penetration Conference
La Grande Motte, France – April, 2018

Speaker Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objectives

- To identify the interaction of FDA regulatory Centers and the jurisdiction for dermatologic products, including generic drugs
- To help initiate our meeting‘s dialogue about penetration of generic drugs and other substances thru the skin by having an understanding of the underlying anatomy and physiology of this important organ.
- To understand the basics of skin anatomy, physiology and disease in the context of drug, especially generic drug, and medical device development

FDA Dermatology Product Foci

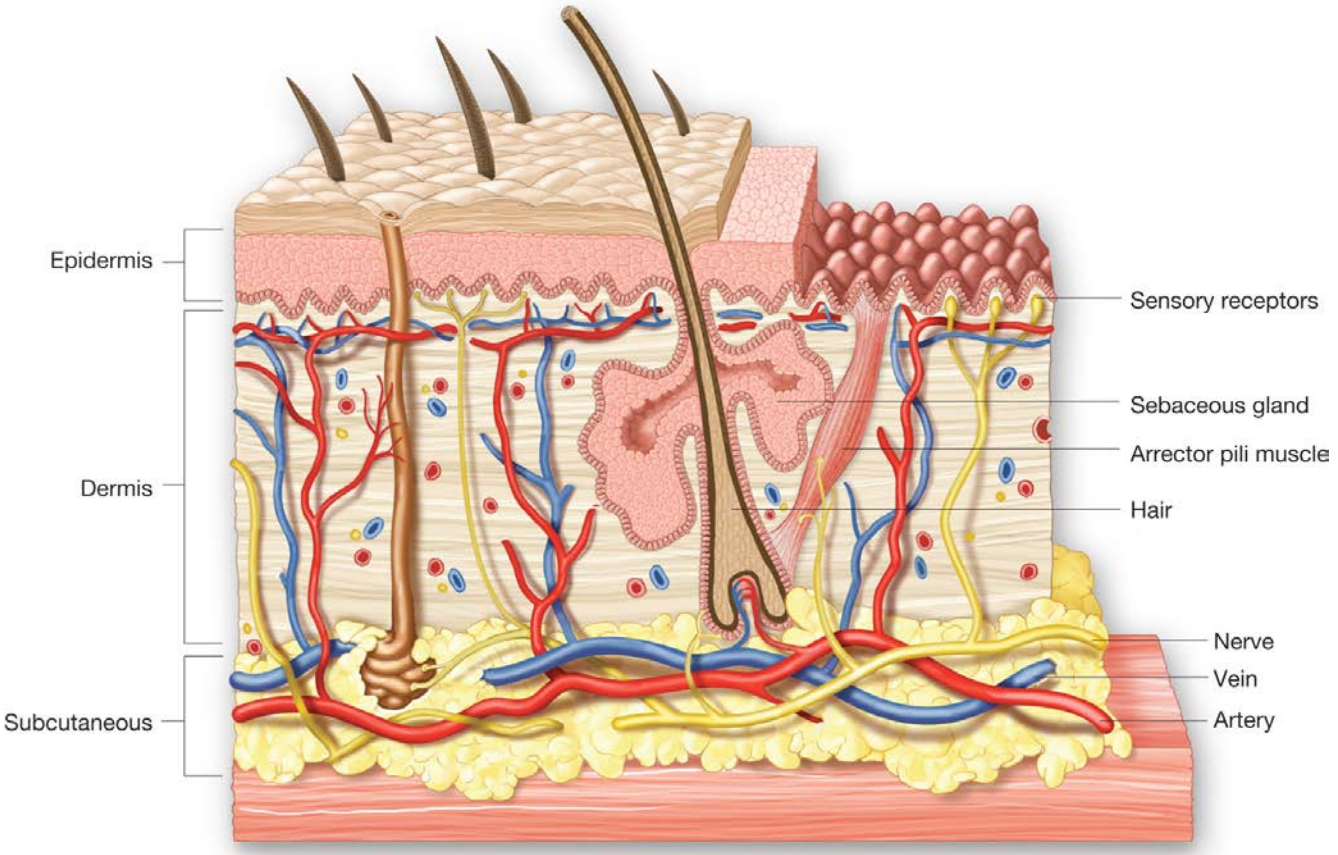
- Center for Drug Evaluation and Research
  - New drugs, Generic drugs
- Center for Biologic Evaluation and Research
  - Vaccines – Allergy testing, Skin Biome
- Center for Devices and Radiological Health
  - Surgical tools, lasers, fillers, implants
  - Diagnostics
- Center for Food Safety and Nutrition
  - Cosmetics

Combination Drugs cross Centers and may combine treatment modalities and technologies

Drug Bioequivalence and Skin

- Generic drug bioequivalence* –
  - Pharmacologic equivalence = “equivalent” delivery of drug to the site of action on/in the skin
  - Therapeutic equivalence = equivalent function of the drug product towards clinical outcome
- A deep understanding of skin anatomy and skin (patho-)physiology is critical to facilitate product development in this arena.

*See 21 CFR 314.3 for official established regulatory definitions.

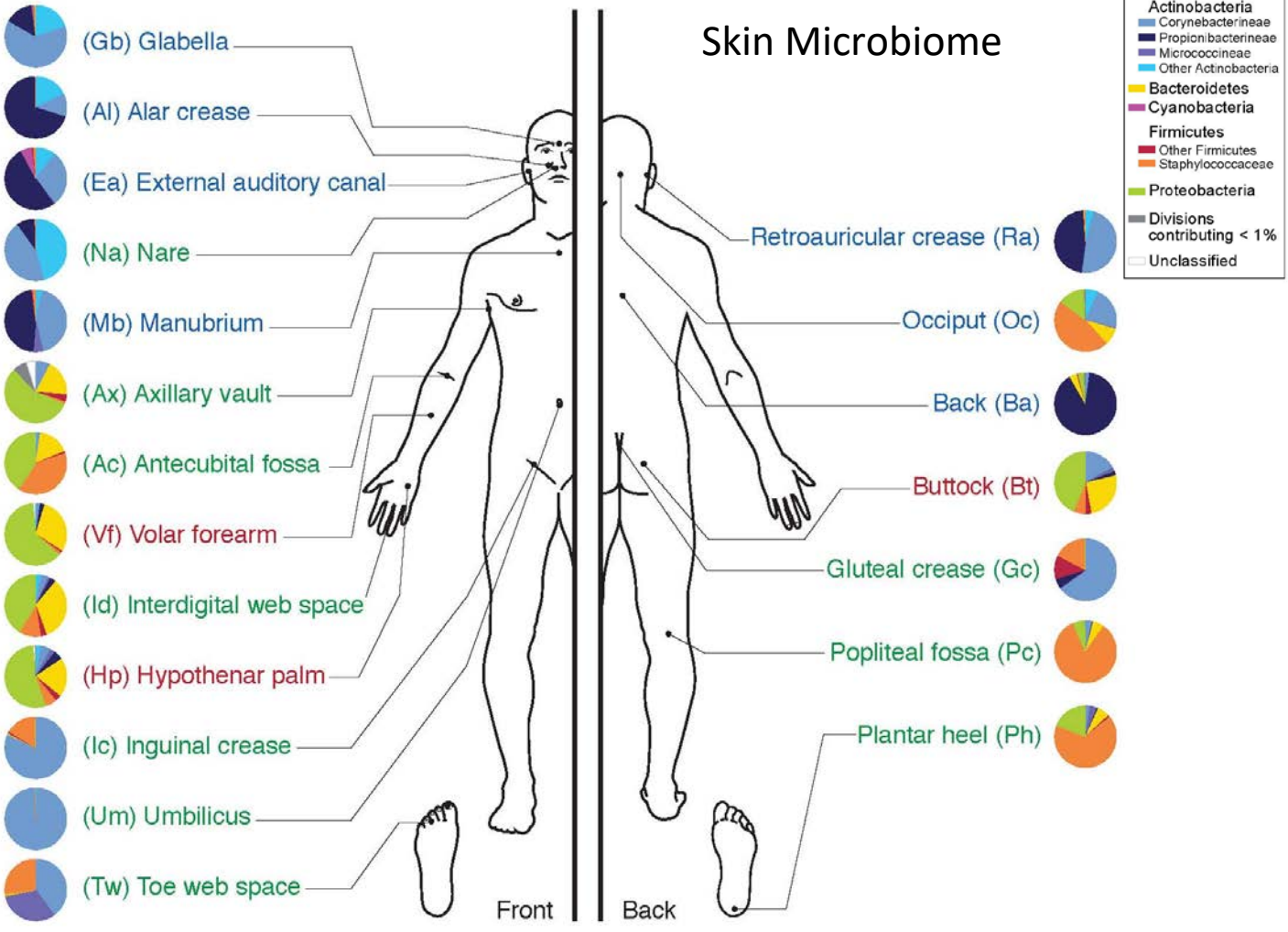

Epidermis
Dermis
Subcutaneous
Sensory receptors
Sebaceous gland
Arrector pili muscle
Hair
Nerve
Vein
Artery

Epidermis

- Stratum corneum is made of keratinocytes, some which keratinize (differentiation process that begins at the basal layer)
  - Acts as a barrier to penetration
    - For transdermal systems (patches) may be a substrate for adherence/interaction with adhesive
    - Major barrier component
    - Top most layer is not flat
    - Gyri and sulci (implications for tape stripping)
    - Invaginations and protrusions such as hair, sweat glands
  - Can act as a reservoir for chemicals, including drug active ingredients
  - This is often the target for generic drug comparison, i.e. use of intact stratum corneum as modeling premise


SEM x50 Human Skin - Back of the Hand
gettyimages
Dr. Wolf Fahrenbach
vis900331

Skin Microbiome



Skin Biome Products

- Modification of the skin biome with specific strains of bacteria, other organisms, manipulation of the biome via bacteriophages are all considered new Biologic products by FDA CBER.
- Investigations on skin biome manipulation by introduction or replacement of organisms require an IND with FDA CBER.
- Some drugs that may impact the skin biome include topical antibiotics, topical antiseptics, topical antifungal agents, and products that may decrease immune surveillance. These are regulated by CDER and include generic drug formulations of these products.

Stratum Corneum

- 15 to 20 layers of flattened cells with no nuclei
- 10 to 40 uM thick
- 14 day migration for a cell to rise from the basal layer to the top of the stratum corneum

Contains Nonbinding Recommendations

Draft – Not for Implementation

Regulatory Considerations for Microneedling Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on September 15, 2017.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Office of Device Evaluation, Division of Surgical Devices, at (301) 796-6970.

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

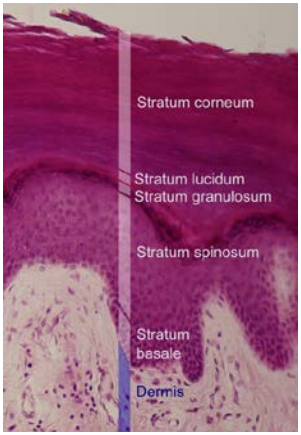
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Physical methods for penetrating skin

- Microneedling products indicated for use with topically applied substances such as creams, ointments, gels, solutions may be regulated as combination products.*
- Manufacturers of such products should contact the Agency for regulatory pathway (513(g) and RFD).
- While there are no currently approved products in this arena, there have been published studies toward the goal of developing such products.
- Variation in needle penetration, size, skin type, etc. may affect drug penetration.

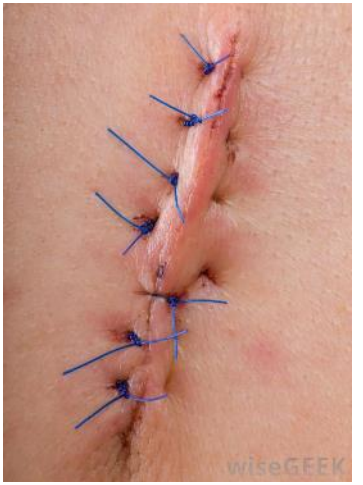
*

Barrier Functions



- Protection from the Environment
  - UV protection
    - Pigmentation
    - Ability to tan
  - Repair mechanisms/wound repair
  - Dermal-Epidermal Junction – Basement membrane – Shear resistance
  - Pathogens
    - Natural skin flora - not sterile
    - Immune system

Dermis



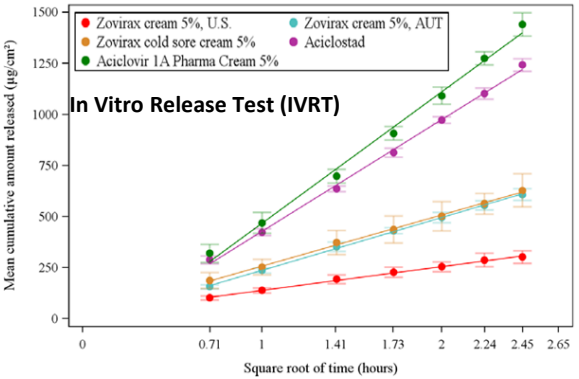
- Lymphatics
- Fibrocellular matrix
  - Superficial anchor for sutures
  - Target for collagen damage/repair (e.g. aesthetic indications)
  - Dermal fillers
- Nerves and blood vessels

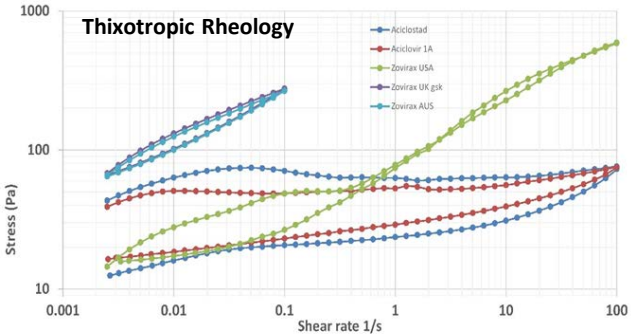
An example of a generic drug workup – Acyclovir Cream 5%

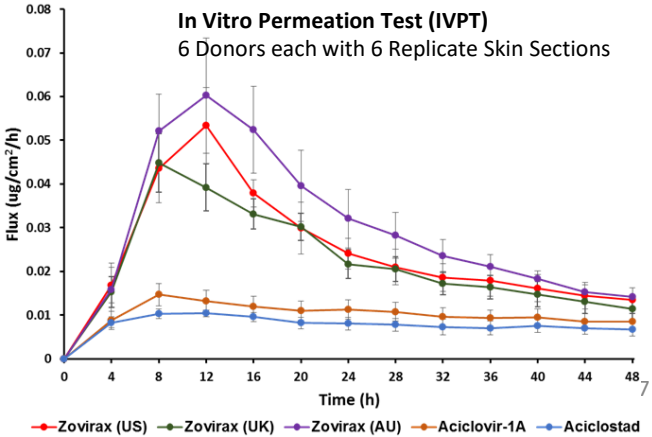
- Product physicochemistry
- Skin pharmacokinetics
- Skin anatomical features that lend to depth specific sampling – rationale for in vivo dermal microdialysis
- Potential utility for future generic drug development

Acyclovir Cream 5%

	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystalline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95







In Vivo Dermal Microdialysis (dOFM)

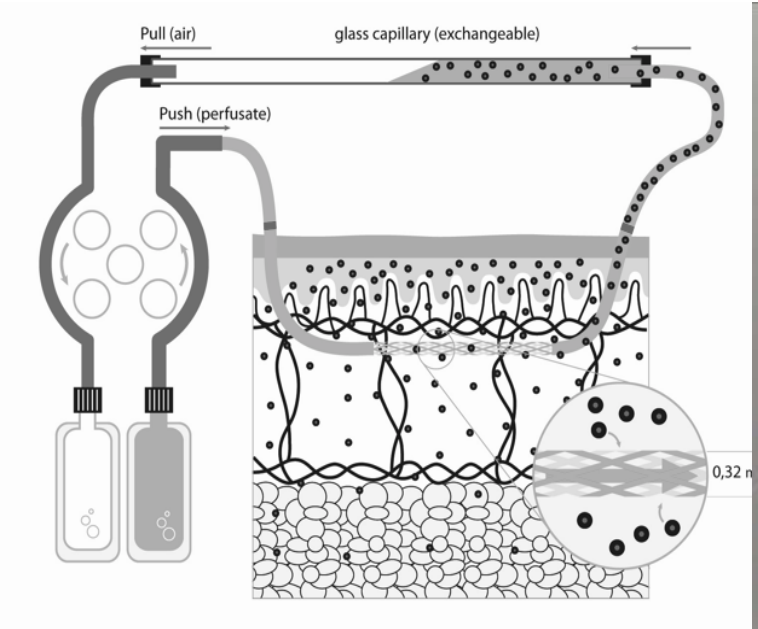
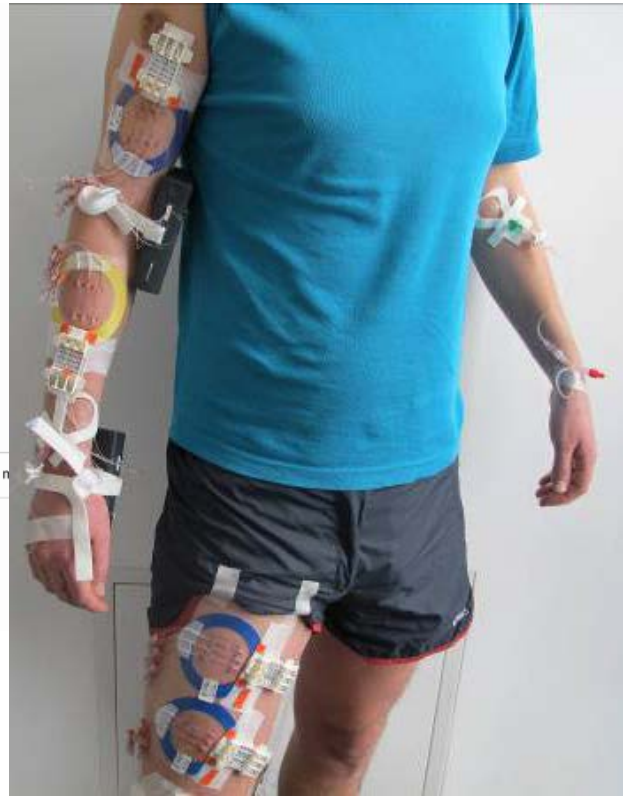
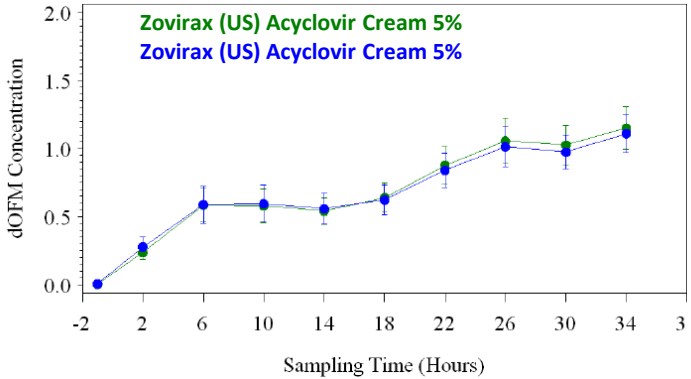


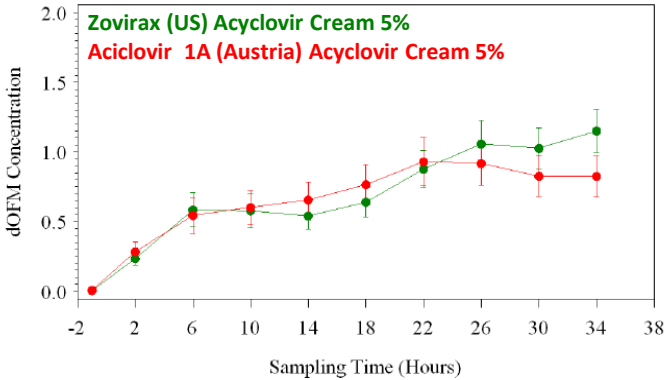
Image courtesy of Joanneum Research



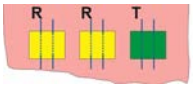
Acyclovir Cream 5% *in vivo* BE

- Dermal Pharmacokinetics by dOFM (20 subjects)





Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]
log(C_{max})	[-0.155 ; 0.190] or [85.7 % ; 120.9%]



JOANNEUM RESEARCH HEALTH

Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]
log(C_{max})	[-0.498 ; 0.022] or [60.8 % ; 102.2%]

Sampling Interstitial Dermal Fluid for Drug Levels

- Removal of fluid – “sampling” thru inserted tubes or needles and measuring drug concentration
  - Limitations include LLQ, contamination, inaccurate location
- In situ measurement (thru confocal [Raman] spectroscopy)
  - Yet to be developed technology
  - Limitations include background noise, top skin reservoir signal

Dermal Fillers (Class 3 medical devices in US)

Material	Description	Depth of Implantation	Duration
Collagen	Bovine or Human Cell	Superficial to deep dermis	3 to 4 months
Hyaluronic Acid	Polysaccharide that gels with water. Sourced from bacteria or rooster combs. May be crosslinked to reduce degradation.	Superficial to deep dermis	6 to 12 months
Calcium hydroxylapatite	Mineral found in teeth and bones. Suspended in gel-like solution for injection	Subdermal to intramuscular	18 months
Poly-L-lactic Acid	Biodegradable man-made polymer (PLLA). Also found in absorbable suture material.	Subdermal	Up to 2 years
Poly-methylmethacrylate beads	Also known as PMMA microspheres. Non-biodegradable man-made polymer. Bead are suspended in a collagen gel-like solution	Deep dermis to subdermal	"permanent"
Autologous Fat	Harvested autologous fat from different site in the recipient (e.g. from liposuction) that is prepared for injection.	Deep dermis to subdermal	Months to years

*not all of these sites are correctable with dermal fillers

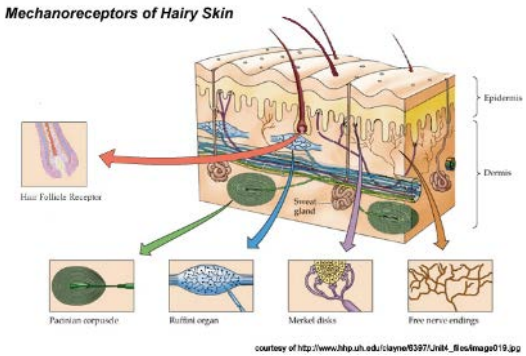
Hypodermis

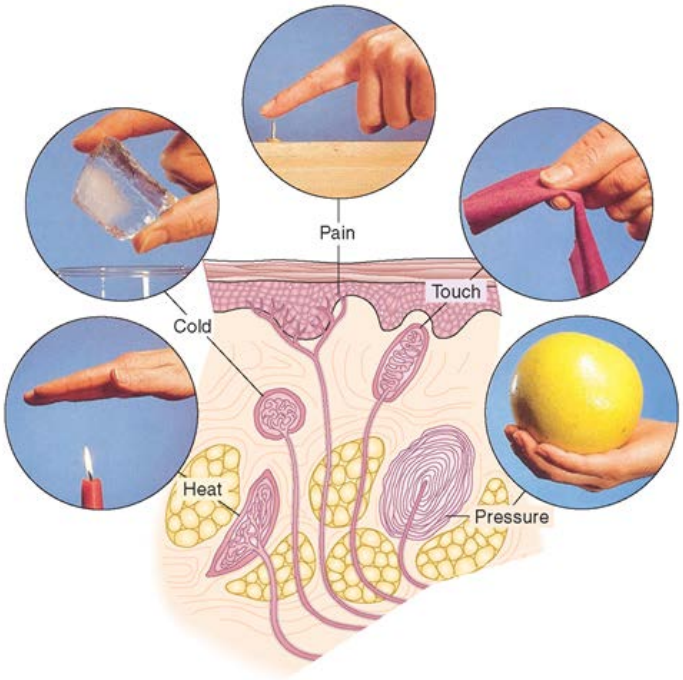
- Fat
  - Energy storage (also drug lipid partitioning)
  - Insulation
- Mechanical Integrity
- Larger “source” vessels and nerves
  - Transcutaneous technologies/catheters
  - Unclear how much transcutaneous drug penetration occurs at this level vs. dermis

Neurosensory Function

- Mechanoreceptors – touch
- Pain
- Temperature
- Itch

* Anesthetic drugs

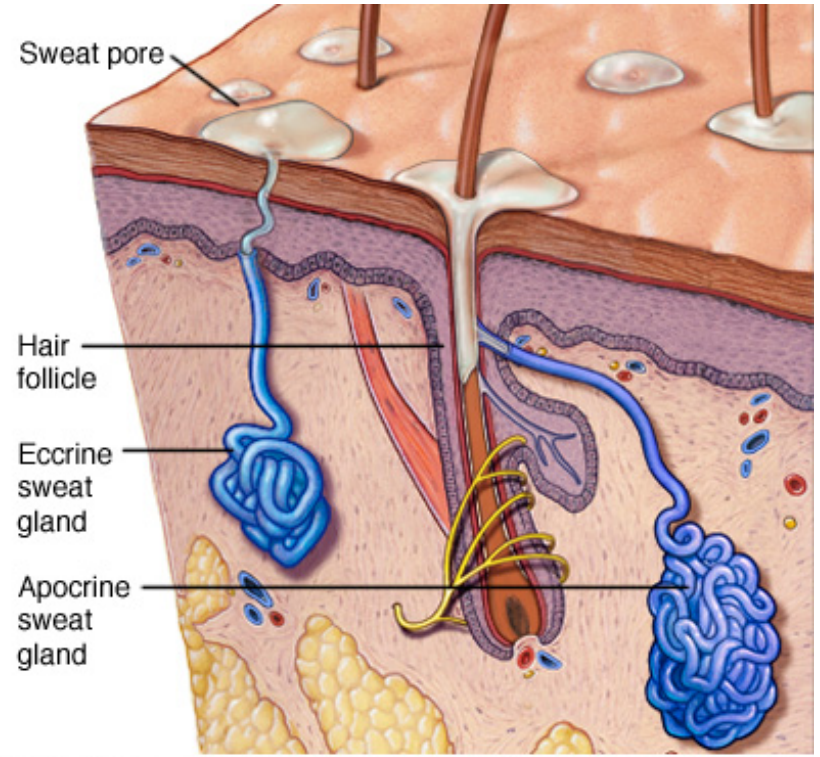




Sweat Glands

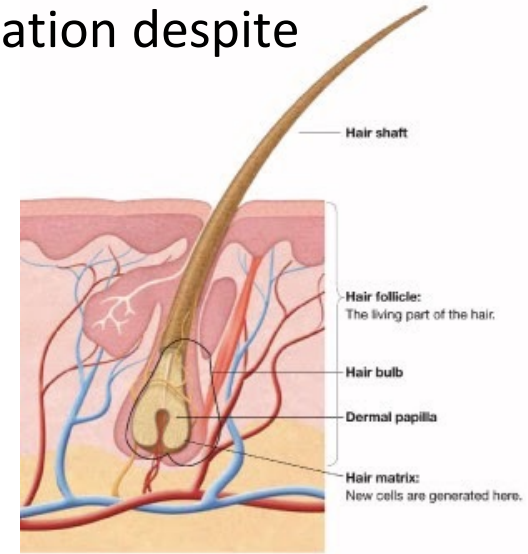
- Skin Surface Moisture
- Biocompatibility considerations
  - pH, skin and skin flora enzymes, chemical reaction with excipients and device materials
- Effect on adhesives and adhesion

Sweat Glands



Hair

- Skin stem cells and hair matrix lie deeper than the skin surface
- Allows for skin and hair regeneration despite superficial injury

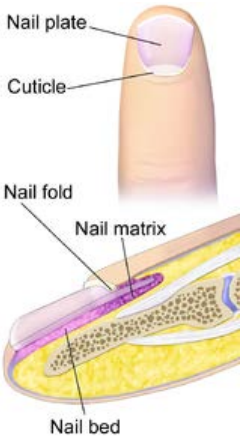


Artificial Hair

- Prosthetic hair fibers are banned medical devices as per 21 CFR 895.101
- Risks outweigh any possible benefit
- Risk of Injury
  - Recurrent infections
  - Rejection and periodic loss of fibers needing frequent replacement
  - Frequent allergic reactions leading to severe contact dermatitis, irritation
  - Cicatricial alopecia
  - Granulomatous hypersensitivity (scar tissue)
  - Cyst formation

Nails

- Nails are horn-like coverings of keratin for the tips of fingers and toes, similar to claws in other animals.
- Knowledge of nail anatomy is essential when evaluating technologies intended to treat diseases of the nails and surrounding tissue.
- Because nails are so slow to grow, new drug clinical effectiveness studies can take a long time (typical outcomes assessment is at a year).
- Generic development for certain nail drugs may be able to avoid comparative clinical endpoint studies by relying on physicochemical characteristics and drug composition.

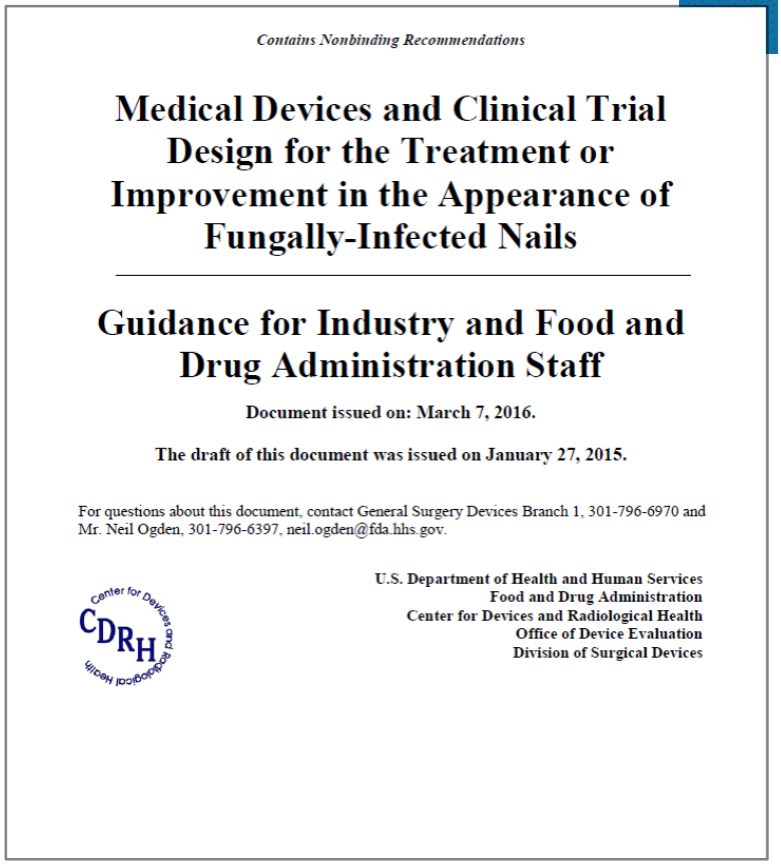


Nail Anatomy

Drugs for treatment of nail fungus

- In general, drugs that target nail fungus need to penetrate the thick keratin plate that is the nail to target living fungal elements that penetrate into the noncellular material.
- In addition, these drugs may go around the nail into the nail bed and target organisms that reside under the nail.
- These are important considerations for developing or matching anti-nail fungus treatments, i.e. viscosity, solvent penetration, and other relevant factors.

Reviews of products intended to treat the appearance of fungally-infected nails (onychomycosis) resulted in the need for a guidance document that spells out specific issues related to how these products should be developed.



Contains Nonbinding Recommendations

Medical Devices and Clinical Trial Design for the Treatment or Improvement in the Appearance of Fungally-Infected Nails

Guidance for Industry and Food and Drug Administration Staff

Document issued on: March 7, 2016.

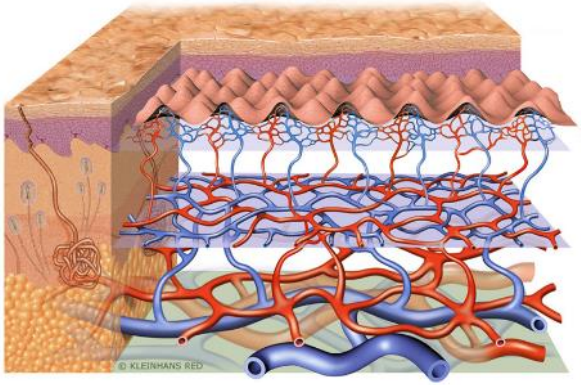
The draft of this document was issued on January 27, 2015.

For questions about this document, contact General Surgery Devices Branch 1, 301-796-6970 and Mr. Neil Ogden, 301-796-6397, neil.ogden@fda.hhs.gov.

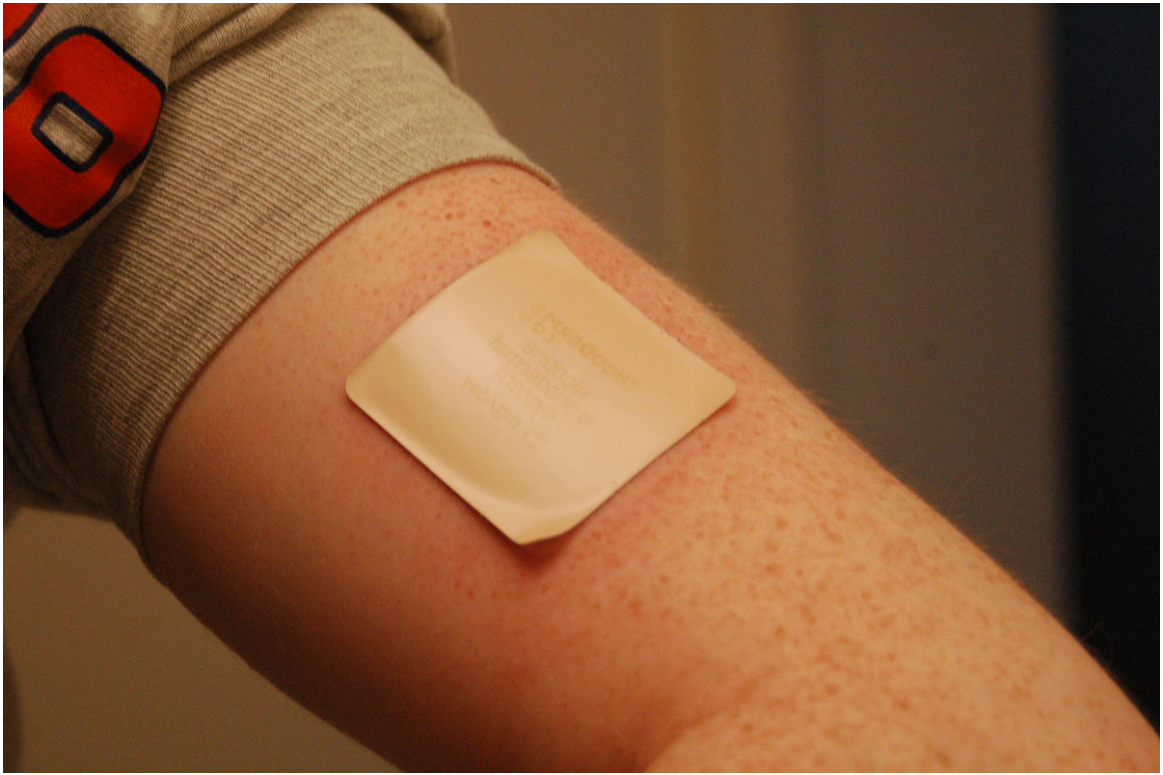
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Division of Surgical Devices

Skin Blood Vessels

- Provides nutrients
- Conduit for immune cells
- Circulatory heat sink (peripheral blood flow)
- Lymphatics regulate interstitial fluid pressure
- These are the target for transdermal drug delivery



Transdermal Systems (Patches)



Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs

Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Kris Andre at 240-402-7959.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2016
Generic Drugs

Currently available PSG's for TDS

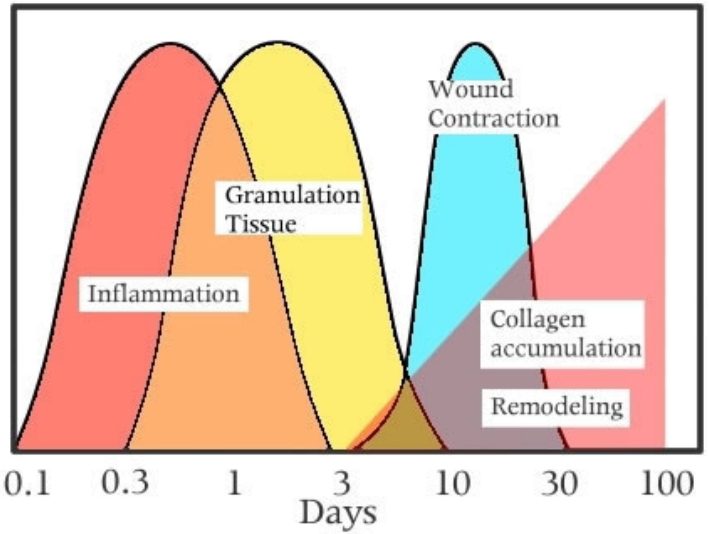
Transdermal delivery systems	Topical delivery systems (patches)
Buprenorphine	Diclofenac epolamine
Clonidine	Lidocaine
Estradiol (4 PSG's for 4 RLDs)	Menthol, methyl salicylate
Ethynil estradiol, norelgestromin	
Fentanyl	
Granisetron	
Methylphenidate	
Nicotine	
Nitroglycerin (2 PSG's for 2 RLDs)	
Oxybutynin (2 PSG's for 2 RLDs)	
Rivastigmine	
Rotigotine	
Scopolamine	
Selegiline	
Testosterone	

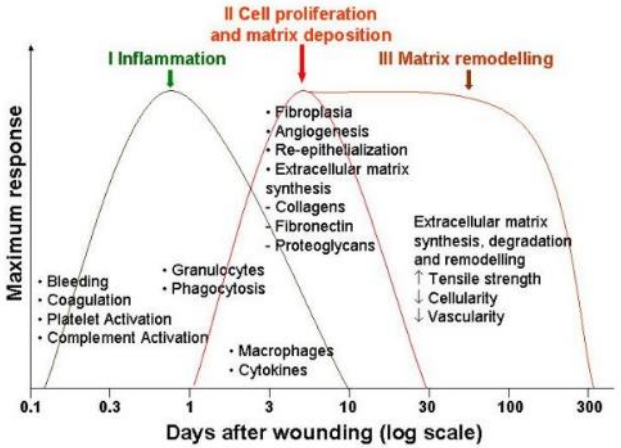
Cutaneous Immune Reactions

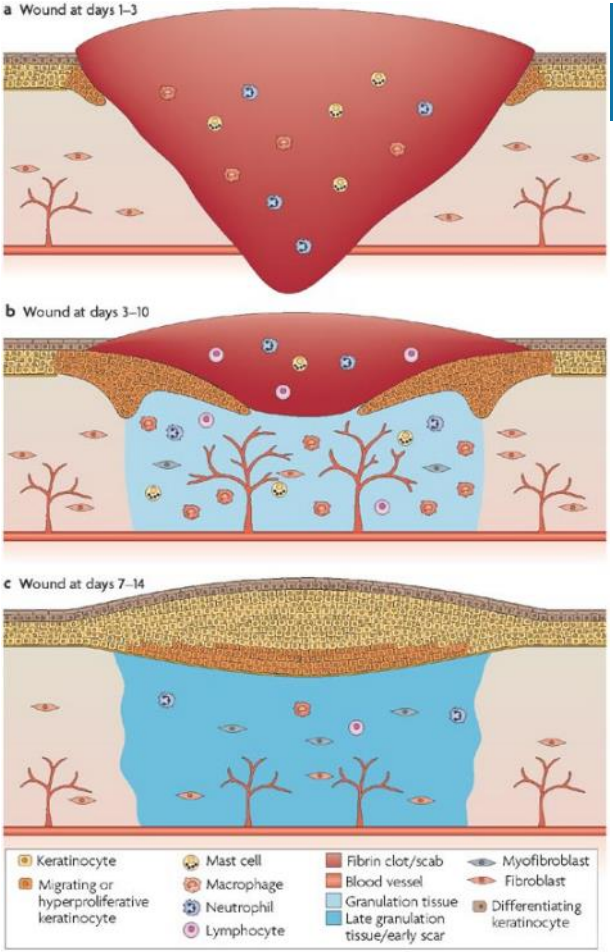
- Systemic allergy
  - Can result in skin manifestations - e.g. hives, skin appearance (tumor, rubor, calor).
- Allergic dermatitis
  - Skin is likely to be the physical interface with the device (patient, user, operator).
- Irritation/sensitization studies are important for topical drug new product development

Wound repair

- Wounds are breaches of skin integrity
- Surgical vs. ulcer vs. laceration
- Chronic vs. acute
- Skin transplantation
- Skin substitution products

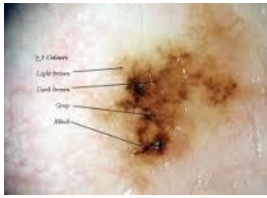






Nature Reviews | Molecular Cell Biology

Skin visualization/spectroscopy



- Diagnosis of skin lesions and skin spectroscopy is a developing arena - potentially a very important area for dermatopharmacology
- How do you “see” thru the layers of reflectance? - liquid medium or polarized light, red>>blue
- Automated comparisons to databases using pattern recognition algorithms
- Cleaning up spectroscopic noise when identifying chemical signals.

Disease effects on Skin Physiology

- Skin – intact or not
- Underlying disease can affect skin structure and drug absorption
- Physical interaction with diseased skin can result in different outcome than healthy skin
  - Weaker skin integrity
  - Surface wet/dry, scaling, roughness, other

Disease and topical drug bioequivalence

- When evaluating for drug going to where it needs to go in diseased skin, we are comparing
  - How the drug passes thru intact portions of skin
  - How the drug passes thru gaps/healed and partially healed wounds in the skin
  - How the drug passes thru skin thickened due to fibrosis, inflammation, hyperkeratinization.

Product Specific Approach

- FDA publishes Product Specific Guidances (PSGs) to provide recommendations on the most sensitive, accurate, and reproducible methods for establishing bioequivalence for a particular listed drug.
- Examples of unique skin or thru skin targeted PSGs:
  - Acyclovir Ointment – Q1/Q2/Q3 + IVRT
  - Acyclovir Cream – Q1/Q2/Q3 + IVRT + IVPT
  - Dapsone Gel – Q1/Q2/Q3 + IVRT + IVPT + PK
  - Buprenorphine TDS – PK + Adhesion + Irrit/Sens

Draft Guidance on Acyclovir

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Acyclovir

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product the following criteria should be met:

A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards,* Revision 1 (May 2015).[1]

B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product.

C. The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.

D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

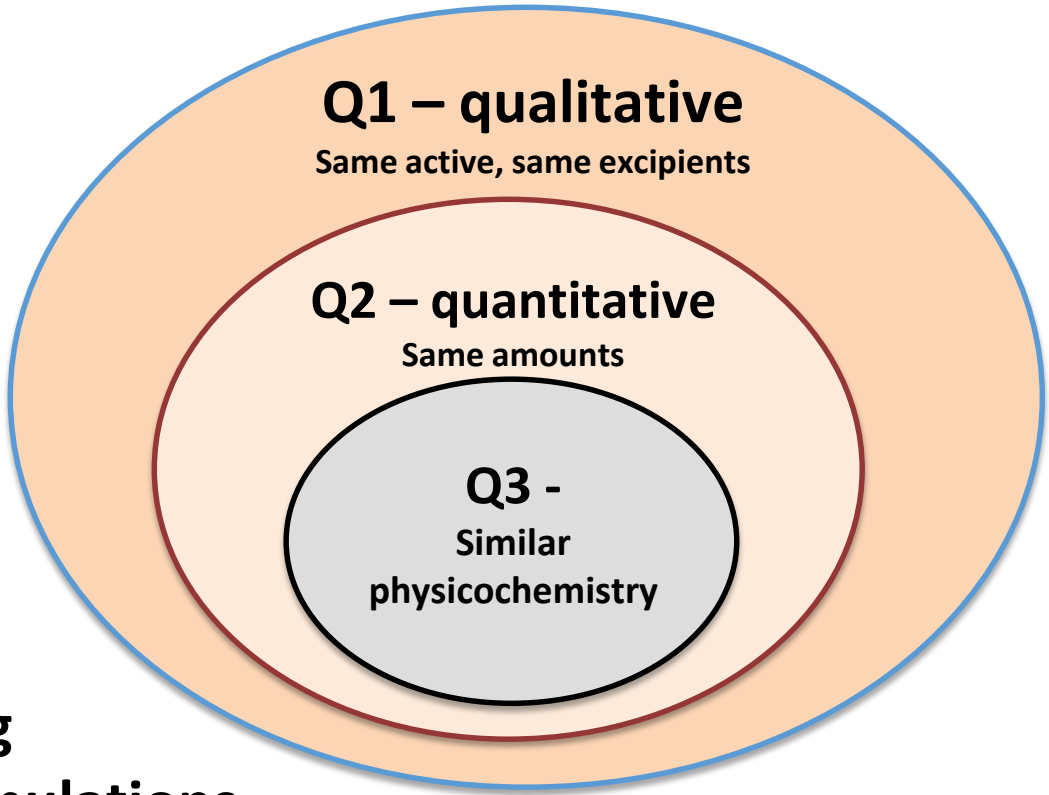
Additional comments: Specific recommendations are provided below.

[1] Guidance for Industry ANDA Submissions – Refuse-to-Receive Standards, Revision 1 (May 2015)

2. Q1, Q2, and Q3 Definitions

- Q1: Same components – Qualitative sameness
- Q2: Same components in same concentration – Quantitative sameness
- Q3: Same physical and structure qualities that define a product
  - Q3 is an in vitro characterization-based determination
  - “Look and feel” can affect how the product sticks to diseased skin
  - Physicochemical differences usually come from manufacturing processes or excipient sourcing if Q1 and Q2 attributes are the same

Q Sameness/Similarity



Drug Formulations

Generic Q Hypotheses

- Even if a topical product (usually a semi-solid) is Q1 and Q2 the same, it can have sufficiently different physicochemical attributes to be noticeable in the clinical context (look and feel) and affect product performance.

- If a test product is Q3 the same as a reference product, it is likely considered to be bioequivalent (greater confidence in inferring BE)

Conclusions

- It is important to understand the anatomy and physiology of the skin in the context of –
  - Regional variation
  - Skin substructures
  - Therapeutic modalities for diseases
- Key issues regarding biocompatibility, barrier function, selective tissue targeting, visibility, and interfacing of this important organ with various therapeutic products.

Questions?

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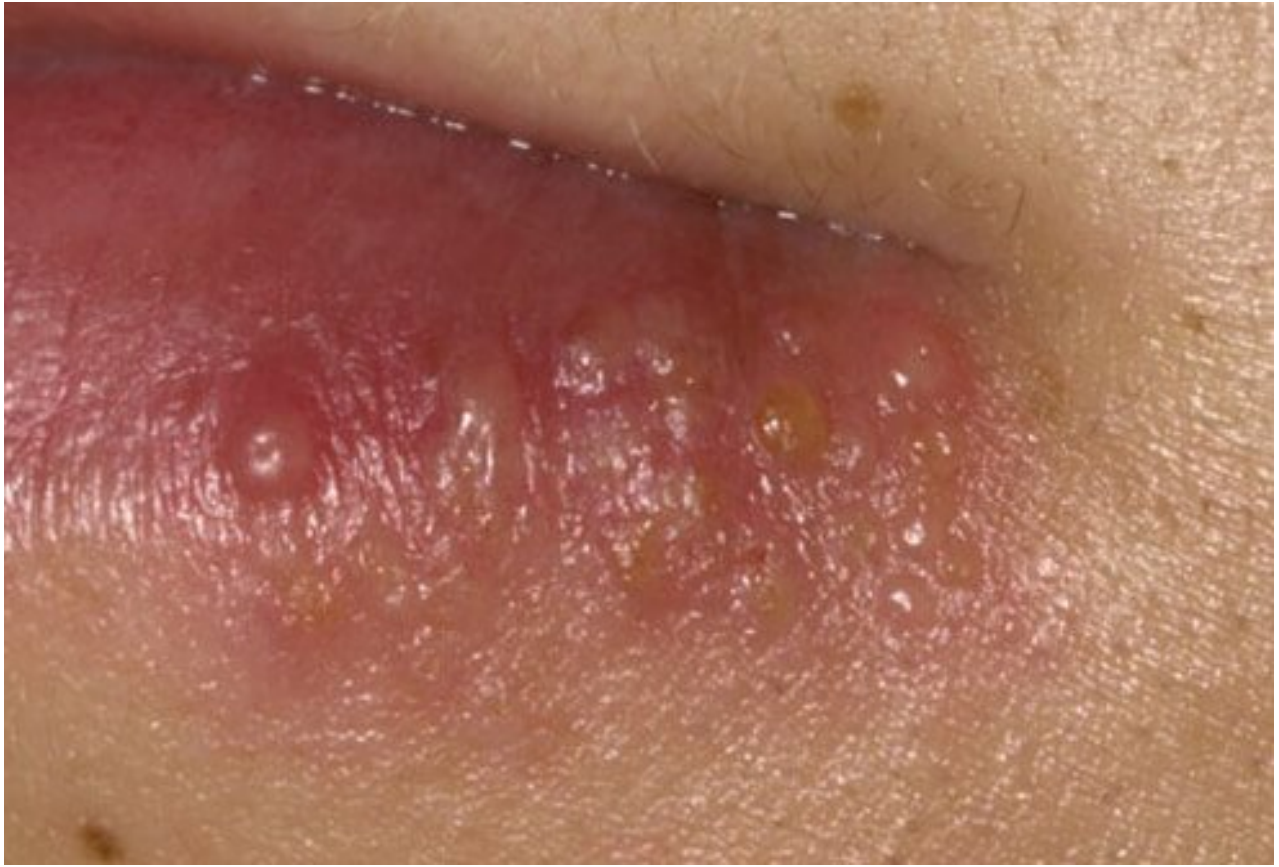
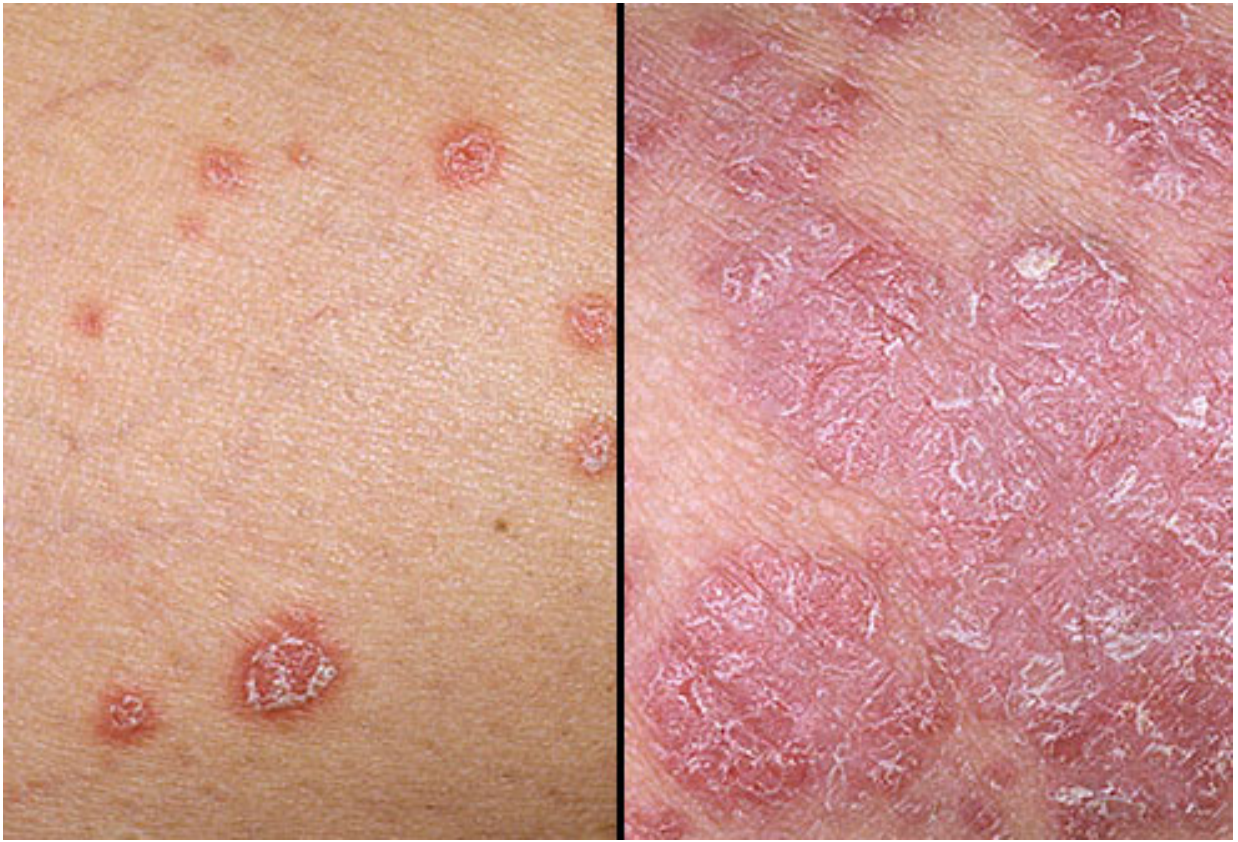
Extra slides

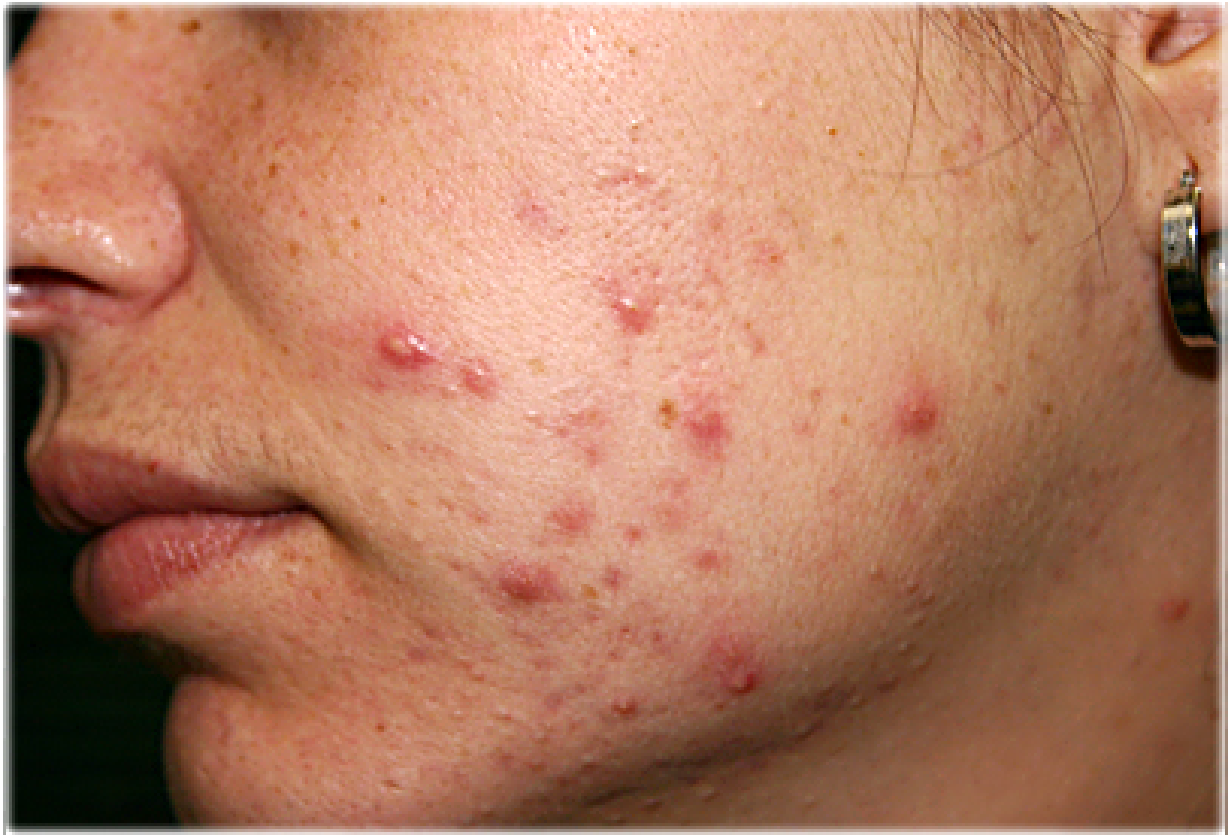
Herpes simplex 1 (Cold sores)



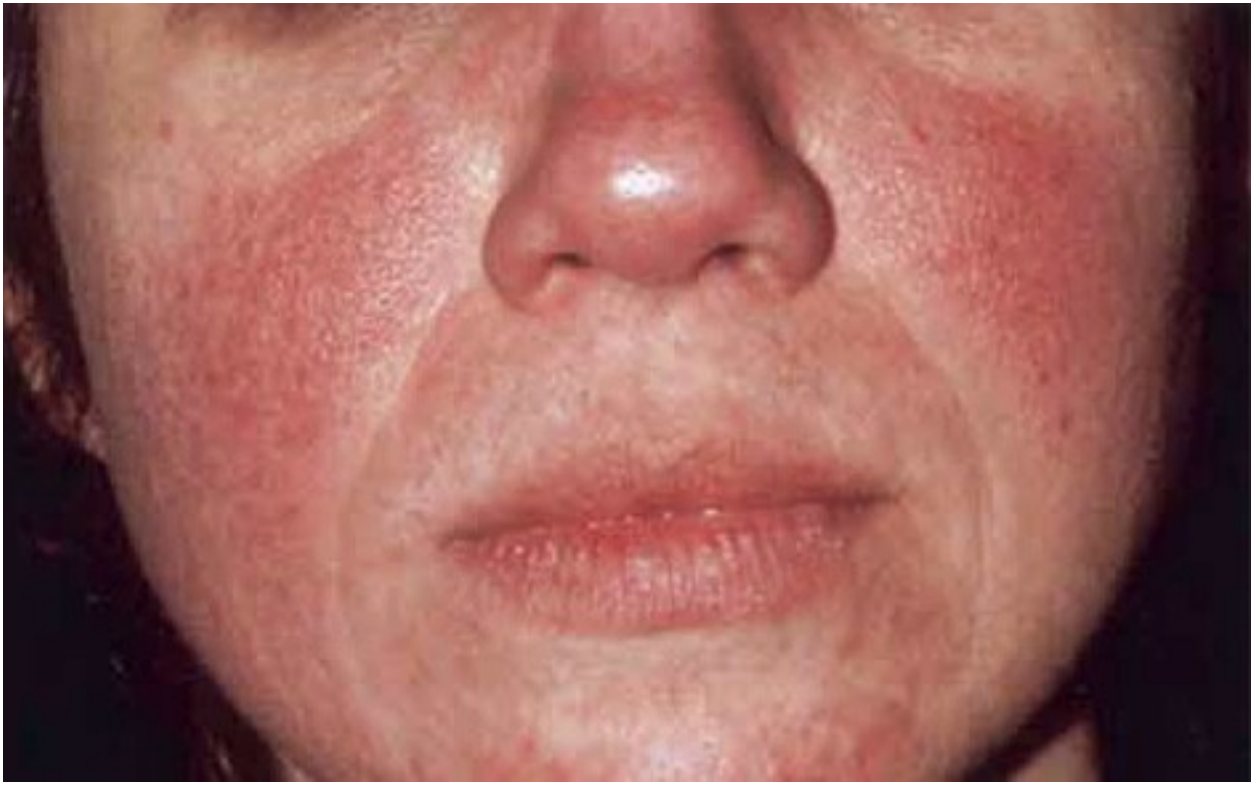
Psoriasis



Acne vulgaris



Rosacea

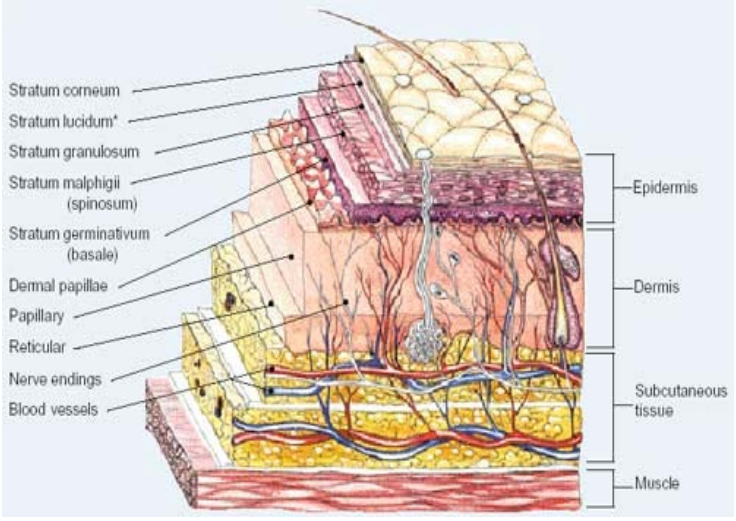


Aesthetic Function of Skin, Hair, Nails

- Physical appearance
- Genetics
- Race
- Social factors

Skin Composition Heterogeneity

- Different parts of the skin absorb energy/light differently
  - How superficial
  - Color
  - Water composition
  - Lipid composition

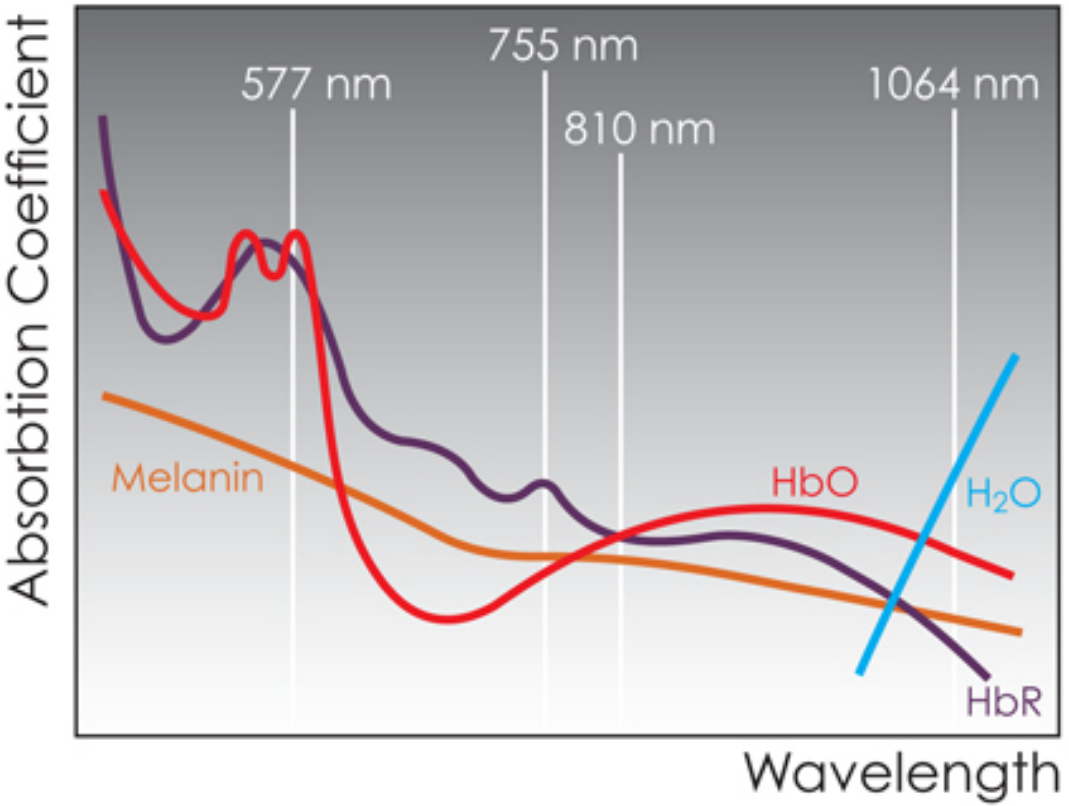


Skin composition heterogeneity

- Laser Selective Photothermolysis
  - Melanocytes
  - Colored hair
  - Water content
  - Skin surface cooling
- Microwave devices – target H_2O
- Cold devices – selective freezing

Laser Therapy

Differential Chromophore Absorption



Output by Laser Type