



# To and Thru the Skin

## *Transdermal and Topical Delivery of Dermaceutical and Cosmeceutical Products: United States Legal/Statutory Scenario*


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# Agenda

- Drugs versus Cosmetics (“Cosmeceuticals”);
- Non-Patent Market Exclusivities;
- Bioequivalence Approaches, Inactive Ingredients, Labeling and Other Regulatory Issues;
- Fentanyl, Lidoderm, Efudex.

# “Cosmeceuticals”

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- Cosmetics industry uses term “cosmeceuticals” to refer to cosmetic products that have medicinal or drug-like benefits such as
    - Alpha Hydroxy Acids (“AHA”)
      - Products containing AHAs intended as acne treatments or skin lighteners (skin peeling agents) are drugs;
      - Products containing the AHAs glycolic and lactic acid are cosmetics if
        - Intended as a mild skin exfoliant;
        - the AHA concentration is 10 percent or less.
    - Products containing salicylic acid
      - Used as an active ingredient in acne products regulated as an over-the-counter (OTC) drug;
      - Used as a cosmetic ingredient in many cosmetic cleansers and peels.

# Cosmeceutical Product Examples Cont.

- Products containing sunscreen ingredients;
  - Some cosmetics contain a sunscreen active drug ingredient which functions as a sunscreen – to absorb, reflect, or scatter the harmful burning rays of the sun – making such products liable to regulation as both drugs and cosmetics, FDC Act § 509; 21 U.S.C. § 359,
  - Other cosmetic products contain a sunscreen ingredient “for nontherapeutic, nonphysiologic uses (e.g., as a color additive or to protect the color of [a] product).” 21 C.F.R. § 700.35(a).
- Cocoa butter, lanolin, mineral oil, and petrolatum;
  - can function cosmetically as skin conditioning agents
  - can function therapeutically as OTC skin protectant active drug ingredients. 21 C.F.R. § 346.14(a).

# Cosmeceuticals Cont.

- No separate category in law for these products: FDA regulates either as drugs, cosmetics, or both, depending on the intended use of the product.
- Congress specifically focused on intended use as the basis for regulating products under the Act. See S.Rep. No. 361, 74th Cong., 1st Sess. 240 (1935) (“The use to which the product is to be put will determine the category into which it will fall.... The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put.”).

# Intended Uses of Cosmetics Versus Drugs

- Drugs are “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” and “intended to affect the structure or any function of the body of man or other animals.” 21 U.S.C. § 321(a)(g)(1).
- Cosmetics are “intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance.” 21 U.S.C. § 321(a)(i).

# Examples of Cosmetic Claims Versus Drug Claims

- Anti-wrinkle products:
  - Drug claims (wrinkle preventing claims):
    - claims that the product will physiologically affect the body, even for a temporary period such as:
      - “counteracts,” “retards,” or “controls” aging or the aging process.
      - “rejuvenate,” “repair,” or “renew” the skin.
  - Cosmetic claims (wrinkle smoothing agents):
    - Claims that a product will temporarily improve the appearance of outward signs of aging.

# 2007 Warning Letter Re Hyaluronic Acid Anti-Wrinkle Products

- On April 24, 2007, FDA sent a Warning Letter to Fusion Brands International SRL objecting to several of the company's claims to promote "LiftFusion" brand products, which contain hyaluronic acid and other ingredients, are drug claims.
- The Warning Letter targeted the following claims:
  - "The first Topical-Injectable alternative to doctor-administered anti-wrinkle injections: proven more effective than Botox in a clinical study";
  - "[H]elps reduce existing wrinkles AND boost collagen to promote skin's natural defenses against new ones";
  - "[D]elivers a powerful blend of anti-aging elements to actively counteract fine lines and deep wrinkles";
  - "[W]rinkle-repairing results are...measurably proven better than Botox in a clinical comparative study";
  - "[S]moothing and lifting to restore skin's youthful firmness";
  - "[V]ertical and horizontal forehead furrows, frown lines, crow's feet and nasolabial lines are...repaired";
  - "[B]locks muscle contractions within 10 minutes of application to the skin which helps to prevent new wrinkle from forming...."

# Drug Approval Routes

- Three statutory paths of drug approval:
  - 505(b)(1) – full reports of safety and effectiveness;
    - New drug application (NDA).
  - 505(b)(2) – some of the data comes from previous findings of safety/effectiveness;
    - A product with some differences from a previously approved product such as a new indication or a combination product.
    - Approval requires clinical data (other than bioequivalence data; “bridging studies”), but others may have conducted the studies.
    - “Paper” NDA.
  - 505(j) – identical to previously approved product
    - Abbreviated New Drug Application (ANDA).
    - Suitability Petition for certain changes.

# Available Non-Patent Exclusivities

- 5-year (New Chemical Entity);
- 3-year (New Use);
- 7-year (Orphan Drug);
- 6-month (Pediatric Exclusivity);
- 180-day (“Generic” Exclusivity).

# Five-Year NCE Exclusivity

- New Chemical Entity (NCE): A drug that contains no active moiety that has been approved by FDA in any other 505(b) application. 21 C.F.R. § 314.108(a).
  - Active moiety is the “molecule or ion...responsible for the physiological or pharmacological action of the drug substance.”
- Runs from the time of approval.
- Prohibits FDA from accepting ANDA or 505(b)(2) application for:
  - Four years if ANDA with Paragraph IV certification;
  - Five years for ANDAs without Paragraph IV certification.

# Three-Year Exclusivity

- 1. Drug application or supplement contains reports of new clinical investigations (other than bioavailability studies) 2. conducted or sponsored by the applicant 3. that were essential to the approval of the application.
- FDA will not approve for three years an ANDA or 505(b)(2) application for the same conditions of approval.
  - Unlike 5-year exclusivity, 3-year exclusivity does not prevent the submission of an ANDA or 505(b)(2) application.

# 3-Year Exclusivity As Applied to Topical Sponge/Antiseptic

- Medi-Flex had NDA for ChloroPrep One Step (chlorhexidine gluconate 2%, isopropyl alcohol 70%), a broad spectrum antiseptic delivered by topical sponge. Colorless product prepares a patient's skin before surgery.
- Company performed clinical trials to support sNDA for ChloroPrep with Tint, which added tint and included 26 ml applicator.
- Tint can help the surgeon to see where a nurse or other practitioner has applied the product. The tint also helps detect pooling.

# Example of 3-Year Exclusivity Cont.

- FDA granted 3-year exclusivity based on sponsor's clinical trials.
  - In 2005, law firm Sidley Austin filed a citizen petition requesting the agency to refrain from approving an ANDA filed by Cardinal Health.
  - Sidley claimed that Cardinal Health improperly tried to circumvent the exclusivity by using the non-protected clear product, rather than the protected tinted product, as the Reference Listed Drug (“RLD”).
  - Sidley withdrew the citizen petition in 2007 and the agency never approved Cardinal Health's ANDA.

# Seven-Year Orphan Drug Exclusivity

- FDA may not approve any application (including a full NDA or BLA) for seven years for the same drug for the same condition or indication. 21 C.F.R. Part 316.
- FDA awards orphan exclusivity to product that FDA designates as an orphan drug product and approves.
- An orphan drug treats a disease that 1. affects fewer than 200,000 patients in the United States or 2. affects more than 200,000 patients in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.

# Pediatric Exclusivity

- FDA extends the exclusivity or patent life of an innovator drug for six months if the innovator performs studies, in accordance with a written request from FDA, of the drug in children.
- Pediatric exclusivity extends the period of time during which FDA cannot approve an ANDA or a 505(b)(2) application for an application containing that active moiety or new condition of use.
- Exclusivity attaches to all the applicant's formulations, dosage forms, and indications for products with existing marketing exclusivity or patent life that contain the same active moiety.

# Pediatric Exclusivity--Example As Applied to Transdermal

- FDA granted pediatric exclusivity for Alza's Duragesic (Fentanyl transdermal system).
  - Alza conducted a study, in response to an FDA request, to evaluate the safety of initiating and continuing treatment with the fentanyl transdermal system in an opioid-tolerant pediatric patient population with chronic pain, to determine the pharmacokinetics of the fentanyl transdermal system in the same pediatric patient population, and to determine an appropriate dosing regimen.

# 180-Day Exclusivity

- 180-day exclusivity prevents the approval of subsequent ANDAs until 180 days after the “marketing” of “the drug” by the “first applicant.”
  - “The drug” includes the listed drug.
  - “First applicant” includes all ANDAs filed on the same “first” day (shared exclusivity for same-day filings).
  - “First applicant” is the first ANDA with a Paragraph IV certification to any patent.

NOTE: NOT applicable to 505(b)(2) applications.


# Forfeiture Provisions

- The Medicare Prescription Drug, Improvement, and Modernization Act (“MMA”), Pub. L. No. 108-173, 117 Stat. 2006 (2003), amended the FDC Act so that the 180-day exclusivity period available to a first applicant can be forfeited if any of several “forfeiture events” occur.
- NOTE: NOT applicable to 505(b)(2) applications.

# Patent Certification Process

- ANDA applicant must submit a certification to each patent listed for the RLD in the Orange Book. 21 C.F.R. § 314.94(12).
- 505(b)(2) applicant must submit a certification to each patent listed for the drug on which investigations that are relied upon by the 505(b)(2) applicant for its application were conducted. 21 C.F.R. § 314.50(i).

# Patent Certification Process Cont.

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- Paragraph I—Patent Information Not Submitted;
    - FDA may immediately grant final approval when otherwise eligible.
  - Paragraph II—Patent Expired;
    - FDA may grant final approval when patent expires
  - Paragraph III—Approval Not Requested Until Date Patent Expires;
  - Paragraph IV—Challenges patent as invalid, unenforceable or not infringed by the ANDA 505(b)(2) application;
  - Section viii Statement for use patents; or
  - “no relevant patents” certification.

# 30-Month Stay

- ANDA applicant must submit notification of paragraph IV certification to brand. Timeframe dictated by MMA.
- Brand-name drug maker has 45-day window to sue.
- Suing within that timeframe will trigger 30-month stay during which the agency cannot grant final approval to the ANDA.
- Amended as part of the MMA generally to allow only one 30-month stay per ANDA or 505(b)(2) application.

# General Requirements of Sameness with RLD

- Generic drug applicant must show proposed product is “the same as” RLD with respect to active ingredient, dosage form, route of administration, strength, and labeling. 21 U.S.C. § 355(j)(2)(A).
  - Suitability petition – pharmaceutical alternative.

# Bioequivalence in General

- A generic drug also must be shown to be “bioequivalent” (BE) to the RLD. 21 U.S.C. § 355(i)(2)(A)(iv); 21 C.F.R. § 314.94(a)(7).
- Rate and extent of absorption of the generic drug do not show a significant difference from the rate and extent of absorption of the RLD when administered under similar experimental conditions. See 21 U.S.C. § 355(j)(8)(B)(i).

# Alternative Methods to Show Bioequivalence

- MMA added a subsection explaining that “[f]or a drug that is not intended to be absorbed into the bloodstream, [FDA] may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.” 21 U.S.C. § 355(j)(a)(c).
- This amendment codified FDA policy whose statutory basis had been the subject of controversy.

# MMA and Bioavailability Cont.

- MMA also added a provision that FDA may assess the bioavailability of non-systemically absorbed drugs “by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action.” 21 U.S.C. § 355(j)(8)(A)(ii).

# Regulatory BE Approaches (21 C.F.R. § 320.24)

- Pharmacokinetic study where drug concentrations measured in plasma or urine;
- In vivo pharmacodynamic comparison;
  - Used for generic topical corticosteroids such as Clobetasol Propionate.
    - See CDER, FDA, Guidance: Topical Dermatological Corticosteroids: In Vivo Bioequivalence (1995).
- In vivo clinical endpoints;
  - Most topicals and non-systemically absorbed drugs.
- In vitro comparison;
- Any other approach FDA deems appropriate.

# BE/Clinical Endpoints for Locally-Acting Drugs

- Clinical endpoints generally required to show bioequivalence of locally-acting drugs such as topicals.
- 3-arm comparative trial: generic, placebo and RLD.
- Trial design and dosing similar to RLD—randomized and blinded.

# FDA Denies Most of Salix Colazal Citizen Petition

- On Dec. 28, 2007, FDA denied Salix Pharmaceutical's request to issue guidance or regulations providing bioequivalence standards for oral, locally acting gastrointestinal drug products prior to approving any ANDAs.
  - FDA: Category of oral, locally acting GI drug products is so diverse that single bioequivalence recommendation not appropriate.
- FDA denied request that any ANDA for an oral formulation of oral drugs containing balsalazide disodium include efficacy evidence from appropriately designed comparative clinical studies.

# Demise of DPK Guidance

- In 1998 FDA issued Draft Guidance for Industry: Topical Dermatological Drug Product NDAs and ANDAs-In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies (June 1998).
- Guidance laid out dermatopharmacokinetics (“DPK”)—attempt to determine bioequivalence of topical skin products based on measurement of the active moiety in the stratum corneum.
- FDA withdrew guidance due to concerns about reproducibility of method. See 67 FR 35122 (May 17, 2002).

# Waivers of In Vivo Study Requirements

- FDA may waive its requirement for in vivo bioavailability/bioequivalence documentation where equivalence is considered “self-evident.”
  - The agency may waive the requirement for a topical skin solution if the product contains no inactive ingredients or other changes in formulation that may significantly affect the absorption of the active ingredients. See 21 C.F.R. § 320.22(b)(3).

# Changes in Inactive Ingredients

## 21 C.F.R. § 314.94(a)(9)(v)

- Generally, drug product intended for topical use, solutions for aerosolization or nebulization and nasal solutions must contain same inactive ingredients as the RLD.
- ANDA for those products may contain different inactive ingredients if:
  - Applicant identifies and characterizes the differences;
  - Applicant provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

# Topicals Mentioned as Part of Critical Path Report

- Critical Path Opportunities for Generic Drugs Report, issued May 2007.
  - Critical Path Initiative established in 2004 to determine obstacles on “critical path” between concept development and approval.
  - Report identifies difficulties establishing bioequivalence for certain drugs including asthma inhalers, nasal sprays, and topical skin applications as barrier to development of additional generics.

# BE and Critical Path Report Cont.

- Report calls for research on new bioequivalence methods tailor-made for each difficult drug class.
- “For topical corticosteroids, pharmacodynamic skin blanching studies are recommended to demonstrate bioequivalence. For most other topical products, lengthy and costly clinical studies are recommended to establish bioequivalence because no alternative methods have been developed.”
  - “Based on the analysis of the mechanisms for topical drug delivery, it may be possible to identify a limited number of key factors that determine product performance and to employ this understanding in the development of rational bioequivalence standards that are much more efficient.”

# FDA Report Identified Following Opportunities for More Efficient BE

- **Design of BE Trials with Clinical Endpoints:**
  - Better understanding of when non-inferiority trial designs can be used.
- **In Vitro Characterization of Topical Dermatological Products:**
  - These tests, including rheological test methods and diffusion cells, may be sufficient to demonstrate bioequivalence of products that have identical amounts of both active and inactive ingredients.
- **Local Delivery of Topical Dermatological Products:**
  - Need for new in vivo tools in the areas of PK studies, skin stripping, microdialysis and near infrared spectroscopy that can demonstrate whether changes in formulation will affect local delivery.

# Same Labeling Requirement and Exception

- Generic drug applicant's proposed labeling must be same as the labeling approved for the RLD except for permitted differences such as those due to a suitability petition and omission of information protected by patent or market exclusivity. 21 C.F.R. § 314.94(a)(8)(iv).
- To approve an ANDA that omits an aspect of labeling protected by patent or exclusivity, FDA must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R. § 314.127(a)(7).

# Lidoderm (Lidocaine) Citizen Petition

- Endo citizen petition (Dec. 18, 2006) (amended version Aug. 29, 2007) urged FDA to:
  - Withdraw lidocaine topical patch bioequivalence recommendations that recommended PK study and skin irritation studies for generic;
  - Decline or stay approval of generic or 505(b)(2) applications that do not have BE studies with clinical endpoints;
  - Convene advisory committees to discuss appropriate method for demonstrating BE for drug products with patch dosage forms and local routes of administration.
- If the agency does craft an alternative method to BE studies with clinical endpoints, FDA should do so through a public process with input from specific advisory committees.

# Lidoderm Citizen Petition Cont.

- Endo claimed that FDA inappropriately applied the standards for transdermals to a topical by not requiring clinical endpoint and instead asking for PK study, skin irritability study, and in vitro dissolution testing.
- FDA issued draft guidance on bioequivalence recommendations for specific products on May 7, 2007. The recommendations are consistent with the proposed testing Endo protested in its citizen petition.
- Citizen petition is still pending with FDA.

# Alza Fentanyl Citizen Petition

- One of 4 citizen petitions seeking additional requirements for all applicants for generic versions of Duragesic Fentanyl Transdermal system.
- Petition urged FDA to require fentanyl matrix system manufacturers to develop comprehensive drug abuse risk minimization programs.
  - Purportedly easier for drug abusers to extract fentanyl from matrix systems (dose dumping) than from reservoir systems.
- FDA should classify matrix and reservoir fentanyl transdermal systems, and products with and without rate-controlling membranes as different dosage forms that are not pharmaceutical equivalents.

# FDA Response to Four Fentanyl Citizen Petitions

- FDA approved Mylan's fentanyl patch ANDA on Jan. 25, 2005.
- It denied all 4 Citizen Petitions in Jan. 28, 2005 letter.
  - Matrix and reservoir fentanyl transdermal systems, and products with and without rate-controlling membranes are all same dosage form:
    - Agency does not base dosage form descriptions on release mechanisms.
  - Not easier to abuse Mylan's product than Alza's, although methods of abuse may differ
    - Gel from the Alza's gel-in-reservoir system may be frozen and broken into small fragments for sharing, or aliquots of the gel may be injected into multiple people.

# FDA Public Health Advisories Warn of Risks Related to Fentanyl

- FDA issued Public Health Advisory on December 21, 2007.
- Builds on prior fentanyl July 2005 Public Health Advisory.
- Doctors inappropriately prescribe medication and patients incorrectly use the patch.
- FDA asked manufacturers to update the information for fentanyl patches and to develop a Medication Guide for patients.

# December 2007 Public Health Advisory: FDA Highlights

- Fentanyl patch should only be used by patients who are opioid-tolerant and have chronic pain that is not well controlled with other pain medications.
- Healthcare professionals who prescribe and patients who use the fentanyl patch should be aware of the signs of fentanyl overdose.
- Patients prescribed the fentanyl patch should tell their doctor about all medications they take.
- Patients and caretakers should be told how to use the fentanyl patch.
- Heat may increase the amount of fentanyl that reaches the blood and can cause life-threatening breathing problems and death.

# Mylan Fentanyl Overlay Citizen Petition and Request for Stay

- Mylan submitted March 16, 2006, petition requesting that FDA require all applicants for fentanyl transdermal systems conduct a study to support the safe use of an overlay with their respective fentanyl transdermal product:
  - Patch must continuously stick to skin to work as designed.
  - Patients allegedly using everything from “athletic tape” to “waterproof band aids” to make sure product stays on skin.
- Mylan submitted July 24, 2007, stay of action.
- Petition still pending, according to FDA website.

# Generic Efudex

- On April 11, 2008, FDA denied Valeant Pharmaceuticals' December 2004 citizen petition that asked FDA to not approve generic versions of Efudex (fluorouracil) Topical Cream unless the application contains data from an adequately designed comparative clinical study conducted in superficial basal cell carcinoma ("sBCC") patients.
- FDA stated that it did not need to establish bioequivalence in every one of Efudex's approved indications and the agency could extrapolate from a study in actinic keratoses patients.
- FDA approved Spear Pharmaceuticals ANDA for Fluorouracil Cream on the same day it denied the citizen petition.

# Generic Efudex Cont.

- Valeant sued FDA 2 weeks after FDA denied the citizen petition and approved Spear's ANDA. FDA asked the court to stay proceedings and refer the matter to FDA, and suspended the ANDA approval.
- On May 30, 2008, FDA reaffirmed its original decision; however, a U.S. District Court for the District of Central California judge had issued a temporary restraining order (TRO) that did not expire until June 18.
- On June 18, 2008, the district court judge denied the motion for preliminary injunction on the grounds that Valeant could not demonstrate a likelihood of success on the merits and the harm to Spears would outweigh the harm to Valeant.
- Spears resumed sales on June 19, 2008. See e.g. *Industry Revolving Door Hits Spear in Nose, But Firm Relaunches ANDA*, the Pink Sheet, June 30, 2008.

# Conclusion

- Locally acting topical drugs have a different measure of bioavailability than systemically absorbed drugs;
  - See e.g. slide presentation of Dale P. Conner, Pharm.D., Director of the Division of Bioequivalence of the Office of Generic Drugs, before the March 12, 2003 Advisory Committee for Pharmaceutical Science (“ACPS”) (“Plasma concentrations are not an accurate measure of drug availability at the site of activity” and “surrogate measures may not always adequately reflect availability at the site of activity” for topical products).
- Generic drug applicants generally will need to conduct clinical endpoint studies to demonstrate bioequivalence;
- Generic and brand-name topical applicants should consider non-patent market exclusivity.



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