

# Glycolic Acid

## **Pharmacy Compounding Advisory Committee Meeting November 3, 2016**

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# Glycolic Acid Review Team

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# Nomination

- Glycolic acid, 0.08% to 70%, has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for topical use in the treatment of hyperpigmentation disorders and photodamaged skin

# Background

- Glycolic acid is currently available in cosmetic formulations (creams, pads, and lotions) and present as excipient in some topical drug products

# Regulatory Definitions: Drugs and Cosmetics



- Whether a product is a cosmetic or a drug under the law is determined by a product's intended use; different laws and regulations apply to each type of product
- A drug is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or an article (other than food) that is intended to affect the structure or function of the body
- A cosmetic is an article (other than soap) 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 appearance
  - Regulated by CFSAN
  - No premarket approval of products or ingredients (except color additives)

# Cosmetic and Drug Uses of Topical Acids

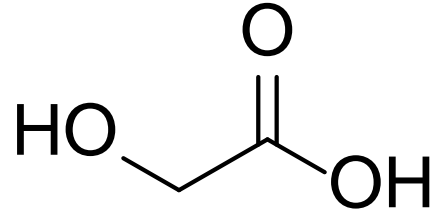


- Topical Acids cause exfoliation, or shedding of the skin surface.
  - The extent of exfoliation depends on the type and concentration of topical acid, its pH, and the other ingredients in the product
  - Examples of topical acids include glycolic, lactic, citric, kojic, and trichloroacetic acid
- Examples of intended use of acids in cosmetics
  - “Smoothing fine lines”
  - “Improving skin texture and tone”
- Examples of intended use of acids in drugs
  - “Hyperpigmentation disorder” or “melasma”
  - “Warts” or “genital warts”

# Physical and Chemical Characterization



- Small organic molecule
- Highly soluble in water
- Easily characterized with various analytical techniques
- No stability issues reported for glycolic acid in the literature
- Likely to be stable under ordinary storage conditions in the proposed dosage forms, such as lotions and gels



# Physical and Chemical Characterization (2)



- Various synthetic routes to prepare glycolic acid
- Likely impurities include:
  - Formaldehyde, monochloroacetic acid (starting materials)
  - Residual reagents
  - Sodium chloride, formic acid, methoxyacetic acid (byproducts from the synthesis process)
- When potential impurities listed above are controlled, the physical and chemical characteristics do not raise significant safety concerns



# Physical and Chemical Characterization (3)



- Summary
  - Based on the available information, there are no concerns about the physical and chemical characterization when potential impurities, such as formaldehyde, are controlled at acceptable levels:
    - well-characterized small molecule
    - Likely to be stable under ordinary storage conditions

# Pharmacology and Toxicology



- Pharmacology
  - One theory for the mechanism of action of alpha-hydroxy acids (AHAs) in exfoliation is: AHAs reduce calcium ion concentration in the epidermis and remove calcium ions from the cell adhesions by chelation; this causes disruption in cell adhesions, and results in desquamation
  - Glycolic acid can suppress melanin formation by inhibition of tyrosinase activity

# Pharmacology and Toxicology (2)



- Safety Pharmacology
  - An intraperitoneal dose of 1000 mg/kg glycolic acid was a potent inhibitor of oxygen consumption and glucose metabolism in rat liver and myocardium in vivo, but did not affect brain oxygen consumption
- Acute Toxicity
  - Glycolic acid in high concentrations (70% solution and pure) causes local effects that are typical of a strong acid, such as dermal and eye irritation

# Pharmacology and Toxicology (3)



- Repeat Dose Toxicity

- In a 3-week dermal toxicity study in hairless guinea pigs, erythema and/or flaking of the skin were noted at 5% and 10% concentrations of glycolic acid
- Glycolic acid was a potent calculi inducer in 4- to 12-week repeat dose oral toxicity studies in rats, with an increase in renal oxalate and nephrotoxic effects
- In a 2-week inhalation toxicity study in rats, respiratory tract irritation, hepatocellular degeneration and thymus atrophy were noted

# Pharmacology and Toxicology (4)



- Genotoxicity
  - Glycolic acid was negative for mutagenicity in the Ames test and the Mouse Lymphoma assay
  - Glycolic acid was negative for clastogenicity in an in vitro chromosome aberration assay and an in vivo micronucleus assay in mice
- Carcinogenicity
  - Glycolic acid did not show photocarcinogenic potential in SKH-1 hairless mice

# Pharmacology and Toxicology (5)



- Reproductive and Developmental Toxicity
  - Oral (gavage) doses of glycolic acid up to 600 mg/kg/day were administered to female rats during gestation days 7-21
  - Maternal toxicity was seen at doses  $\geq$  300 mg/kg/day
  - Developmental toxicity was also noted at doses  $\geq$  300 mg/kg/day, including fetal weight reduction and increases in skeletal malformation

# Pharmacology and Toxicology (6)



- Summary

- There is lack of nonclinical data for the evaluation of chronic dermal toxicity and dermal carcinogenic potential of glycolic acid
- The available nonclinical data do not raise serious safety concerns about glycolic acid when used topically at low concentrations

# Human Safety (1)

- Topical application of glycolic acid enhances photo-irritation by ultraviolet light
  - Because of the potential to enhance sensitivity to sunburn, CFSAN guidance for industry recommends that labeling for cosmetics containing AHAs include a sunburn alert
    - *Sunburn Alert: This product contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen, wear protective clothing, and limit sun exposure while using this product and for a week afterwards*



# Human Safety (2)

- Pharmacokinetic data
  - No reports of human pharmacokinetic studies following topical application
  - In vitro studies indicate pH and time dependence for glycolic acid penetration of skin: ↓in pH or ↑in time of application enhanced penetration

# Human Safety (3)

- FAERS/CAERS Adverse Events Reporting
  - 45 Cases retrieved from FAERS
  - 19 Cases retrieved from CAERS
- Clinical trials - melasma
  - Mainly, local irritancy manifestations such as burning, erythema, swelling and vesiculation
  - Rarely post-inflammatory hyperpigmentation and scarring
- Clinical trials - photodamaged skin
  - Erythema, dryness
- Reported adverse reactions appear to be readily manageable and temporary in duration
- No information on long-term outcomes

# Human Safety (4)

- Alternative Therapies

- Melasma

- The approved drug product, Tri-Luma, is indicated for the short-term treatment of moderate-to-severe melasma of the face in the presence of measures for sun avoidance, including the use of sunscreens

- Photoaging

- Numerous topical retinoids are approved (e.g., tretinoin and tazarotene products) as “an adjunctive agent for use in the mitigation (palliation) of fine facial wrinkles in patients who use comprehensive skin care and sunlight avoidance programs”

# Human Safety (5)

- Summary
  - Available information does not raise major safety concerns associated with the topical use of glycolic acid

# Effectiveness (1)

- Clinical Trials - Hyperpigmentation
  - Literature search revealed multiple reports of studies involving the use of glycolic acid for the treatment of melasma and other hyperpigmentation disorders
  - Most were active controlled trials; there was one trial which included vehicle as control

## Effectiveness (2)

- Clinical Trials – Photoaging
  - Some trials on hyperpigmentation disorders also included endpoints traditionally associated with photoaging studies
  - Two clinical trials specifically addressed the effect of glycolic acid on manifestations of changes associated with photoaging

# Effectiveness (3)

- Summary of Clinical Trial Data
  - Melasma and Other Hyperpigmentation Disorders:
    - Glycolic acid peels of 20% to 70%
    - Improvement with glycolic acid comparable to that with other peels, such as tretinoin, trichloroacetic acid, lactic acid, Jessner solution, or capryloyl salicylic acid

# Effectiveness (4)

- Summary of Clinical Trial Data
  - Manifestations of Changes associated with Photoaging:
    - As a component in Vivite Skin Care System: similar effect on wrinkles when compared to Cetaphil
    - As 8% Cream: superior to vehicle for sallowness and overall severity of photodamage



## Effectiveness (5)

- Seriousness of the conditions for proposed use of glycolic acid
  - Hyperpigmentation disorders and photodamaged skin are not serious conditions *per se*, but pathological changes predisposing to skin cancer may be associated with photodamage

# Effectiveness (6)

- Summary
  - Numerous active controlled trials show consistently positive results in the treatment of melasma with glycolic acid, either as a peel or as a topical agent
  - Overall, the evidence suggests a role for second line treatment of melasma that failed standard therapy or as adjunctive treatment to commonly used topical medications
  - Some evidence from a vehicle-controlled trial may support effectiveness of glycolic acid for mitigation of manifestations of photodamaged skin

# Historical Use in Compounding



- Glycolic acid has been used in pharmacy compounding in the U.S. since at least the mid-1990s
- Uses of glycolic acid have included: ameliorating the appearance of skin aging, melasma and other hyperpigmentation disorders, calluses, keratoses, acne, and psoriasis
- Extent of use cannot be determined; however, countries with reported use include Brazil, Mexico, France, Singapore, Thailand, Korea, India, Turkey
- Foreign pharmacopeias – British, European

## Recommendation

- A balancing of the four evaluation criteria weighs **in favor** of glycolic acid, up to 70%, for topical use, be added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act
- Standard of care for use at strengths of 20% to 70% is in-office application by a licensed health care professional

# Trichloroacetic Acid

## Pharmacy Compounding Advisory Committee Meeting November 3, 2016

Roselyn E. Epps, MD

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# Trichloroacetic Acid Review Team



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DCP3, OCP

**Elizabeth Marek, PharmD**, Historical Use Reviewer,  
OUDLC, OC

# Nomination

- Trichloroacetic acid (TCA) has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act):
  - for topical use in the treatment of common warts (*verrucae vulgaris*)
  - for genital warts (*condylomata accuminata*)
  - as chemical skin peeling agent



# Background

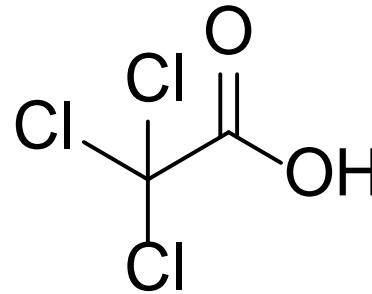
- TCA is currently available in undiluted neat form and at various diluted strengths
- TCA is available in cosmetic formulations and skin peel kits



# Physical and Chemical Characterization



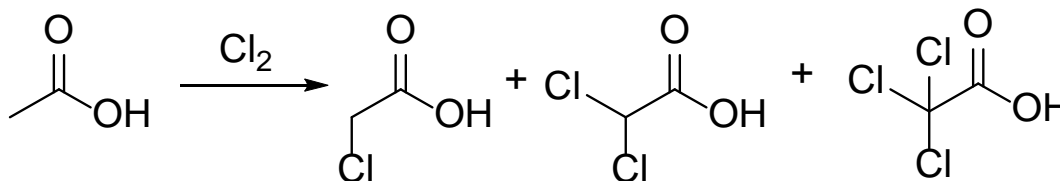
- Small organic molecule
- Soluble in water
- Analog of acetic acid
- Easily characterized with various analytical techniques
- Under refrigeration, TCA is likely to be stable as topical liquid if the pH of the solution is acidic or neutral
  - TCA decomposes when heated, especially in basic aqueous solutions
  - Decarboxylation also occurs under basic conditions



# Physical and Chemical Characterization (2)



- TCA is synthesized via the chlorination of acetic acid to yield a mixture of monochloroacetic acid (MCA), dichloroacetic acid (DCA), and trichloroacetic acid (TCA)



- Likely impurities include:
  - Byproducts (MCA and DCA)
  - Residual starting materials
  - Degradation products (i.e. chloroform)

# Physical and Chemical Characterization (3)



- Summary

- Based on the available information, there are no concerns about the physical and chemical characterization of TCA
  - small organic molecule
  - stable under refrigeration
  - easily characterized with various analytical techniques

# Pharmacology and Toxicology



- Pharmacologic Action
  - Denaturation and precipitation of proteins
- Acute Toxicity
  - Acute oral LD50 in rats = 5000 mg/kg
- Repeat dose toxicity
  - No repeat dose dermal toxicity studies located

# Pharmacology and Toxicology (2)



- Mutagenicity
  - TCA was non-mutagenic in many strains of *Salmonella typhimurium* with or without metabolic activation
  - Positive mutagenicity results have been reported in two strains of *S. typhimurium*
    - Positive results may be due to high concentrations which cause precipitation of proteins

# Pharmacology and Toxicology (3)



- Developmental and Reproductive Toxicity
  - Embryofetal development study conducted in rats with oral TCA administration:
    - Maternal and embryonic toxicity  $\geq 330$  mg/kg/day
    - Embryoletality  $\geq 800$  mg/kg/day
  - High oral doses in rat studies leading to embryotoxicity may not be relevant to topical clinical use

# Pharmacology and Toxicology (4)



- Carcinogenicity
  - No carcinogenicity studies with dermal exposure to TCA located
  - Long-term oral exposure to TCA induced liver tumors in mice, but not rats
  - TCA-induced liver tumors in mice are considered a species-specific effect and may not have clinical relevance
- Toxicokinetics
  - No toxicokinetic studies with dermal exposure to TCA located

# Pharmacology and Toxicology (5)



- Summary

- The toxicity of TCA after topical administration has not been fully evaluated in nonclinical studies
- The available animal data do not raise serious safety issues for topical use in humans



# Human Safety

- Clinical Trials
  - No clinical trials specifically designed to address the safety of TCA
  - Safety assessments were among the study procedures in several clinical trials
- Published reports including FAERS
- Pharmacokinetic data
  - No published reports of human pharmacokinetic studies following topical application of TCA

## Human Safety (2)

- Typical adverse reactions reported with TCA
  - Mild to prolonged erythema
  - Hyperpigmentation and/or hypopigmentation
  - Burning, pain, tenderness, pruritus
  
- Site-specific reactions reported
  - Genital ulcerations
  - Severe vestibulitis
  - Corneal punctate keratitis and conjunctival infection

## Human Safety (3)

- More serious adverse reactions were reported in eye and genital areas
- Adverse events were reported more frequently with higher concentrations
- For localized wart involvement, scars or hypopigmentation were the most frequent sequelae
- Ulcerations were reported in most studies with wart treatment in the genital area

# Human Safety (4)

- Alternative Therapies

- Other FDA approved and OTC therapies are available to treat common warts and genital warts, for example: Salicylic acid; Imiquimod; Podofilox
- Clinical trials directly comparing the safety of TCA to that of FDA-approved treatments for warts are not available

# Human Safety (5)

- Summary

- Clinical trials – genital and common wart treatment

- Adverse reactions included burning, pain, erythema, hyperpigmentation and hypopigmentation
    - More serious adverse reactions reported were ulcerations, scarring, pustules, punctate keratitis and conjunctival infection
    - Adverse events were reported more frequently with higher concentrations

- FDA-approved therapies are available to treat warts

# Effectiveness

- TCA concentration: 10 to 100%
  
- External Genital Warts
  - 5 studies: 4 active control; 1 open label with no comparator
  - Clearance rates varied (31% to 100%)
  
- Common Warts
  - 2 dose-ranging studies; 1 compared to cryotherapy
  - Large variation in response rates (12% to 93%)

## Effectiveness (2)

- Chemical Skin Peeling Agent
  - One of the nominations included two references for TCA potentially related to its use as a chemical peel agent:
    - Atrophic acne scars - Leheta et al. (2011)
    - Melasma - Kumari and Thappa (2010)

## Effectiveness (3)

- Atrophic acne scars:
  - 100% TCA compared to a percutaneous procedure
- Melasma:
  - Dose ranging; compared to glycolic acid, tretinoin
- The design of these studies is such that no conclusion can be drawn



## Effectiveness (4)

- Seriousness of the conditions for proposed use of TCA
  - Generally, common and genital warts are not serious or life-threatening conditions
  - Less commonly, warts may develop into extensive, recalcitrant infections, premalignancies, and carcinomas

# Effectiveness (5)

- Summary
  - No adequate and well-controlled trials evaluating TCA efficacy in the treatment of warts
  - Information from small open label trials suggests some efficacy in wart treatment
    - More efficacious when used at higher concentrations or in conjunction with an additional wart treatment
    - Possible role in treating refractory warts or patients intolerant of other therapies
    - Increase in potential for ulceration and absorption through open wounds with use of higher concentrations

# Historical Use in Compounding



- TCA has documented use in pharmacy compounding in the U.S. for at least 20 years
- Uses of TCA have included: warts, melasma, actinic keratoses, solar lentigines, acne, acne scarring, xanthelasma
- It has been used to treat warts and as a chemical peel for more than 40 years worldwide
- The precise extent of use is unclear
- Foreign recognition includes European and British Pharmacopeias



# FDA Recommendation

- A balancing of the four evaluation criteria weighs **in favor** of the addition of trichloroacetic acid for topical use to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act
- Standard of care for use of TCA in wart treatment is in-office application by a licensed health care professional

# Kojic Acid

**Pharmacy Compounding Advisory Committee Meeting  
November 3, 2016**

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Office of the Center Director

# Kojic Acid Review Team

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**Carmen Booker, PhD**, Pharmacology/Toxicology  
Reviewer, DDDP, ODE III

**Doanh Tran, PhD**, Clinical Pharmacology Team Leader,  
DCPIII, OCP

# Nomination



- Kojic acid, 0.05 to 10%, has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for topical use:
  - in the treatment of hyperpigmentation disorders, and
  - as a chelating agent for wound healing and prevention of photodamage

# Background



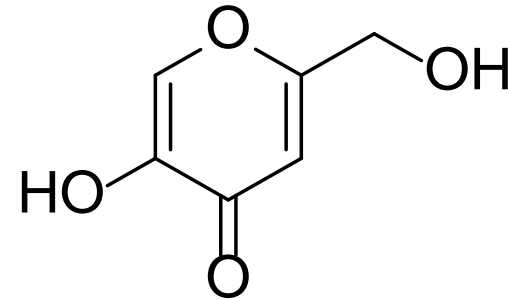
- Kojic acid is currently available in cosmetic formulations (creams, lotions, gels, peels) and in soap bars



# Physical and Chemical Characterization



- Small organic molecule
- Soluble in water
- Naturally occurring chelation agent
- Easily characterized with various analytical techniques
- ***Kojic acid is a very reactive and unstable compound***
  - It oxidizes easily in air, both as a solid or in aqueous solution
  - High temperature, exposure to light, and low pH can all accelerate the decomposition process
  - Requires special sealing and formulation to protect it from decomposition, although the preserving effects are limited



# Physical and Chemical Characterization (2)



- Kojic acid can be obtained from the fermentation of starches and sugars by a variety of microorganisms like *Aspergillus oryzae*
- Likely impurities include:
  - Bioburden (i.e., molds or fungi)
  - Residual starting materials
  - Degradation product(s)

# Physical and Chemical Characterization (3)



- Summary
  - Kojic acid is a small, easily characterized molecule
  - Very reactive and unstable
    - Can affect stability of compounded drug products

# Pharmacology and Toxicology



- Pharmacologic Action – chelator, antioxidant, pigmentation inhibitor, antibacterial, antifungal
- Acute Toxicity – LD50s in rats are 2.6 g/kg (subcutaneous), and  $> 2$  g/kg (dermal and oral)
- Repeat Dose Toxicity – decreased lymphocytes, hematocrit and hemoglobin observed at doses  $\geq 300$  mg/kg; not a skin sensitizer, not irritating to the eyes or skin in animals

# Pharmacology and Toxicology (2)



- Genotoxicity – mutagenicity and clastogenicity observed in in vitro studies; genotoxicity not observed in in vivo studies
- Developmental and Reproductive Toxicity – most studies suggest lack of developmental or reproductive toxicity
- Carcinogenicity – studies are equivocal; carcinogenicity risk is unclear
- Toxicokinetics – dermal absorption is limited; studies in rats showed placental transfer and milk secretion of kojic acid

# Pharmacology and Toxicology (3)



- Summary
  - Limited published nonclinical data on topical use
    - Not irritating to skin or eyes at concentrations up to 3%
    - Not phototoxic at concentrations up to 5%
    - Dermal study in Wistar rats - Mildly decreased lymphocyte counts
    - Genotoxicity observed in in vitro studies; not in in vivo studies
    - Reproductive toxicity - studies suggest lack of developmental or reproductive toxicity
    - Carcinogenicity - equivocal
    - Toxicokinetics – dermal absorption is limited; studies in rats showed placental transfer and milk secretion of kojic acid

# Human Safety



- Adverse events:
  - No events reported in FDA Adverse Events Reporting System or CFSAN Adverse Events Reporting System
    - Possibility that reporting may not be sufficiently descriptive to associate kojic acid with adverse event
  - Published Reports: Clinical Trials & Case Reports
    - Local adverse reactions including irritancy and allergic contact dermatitis
    - No reports of systemic reactions

# Human Safety (2)



- Pharmacokinetics:
  - In vitro study showed that topically applied kojic acid penetrates the stratum corneum of dermatomed skin from healthy donors
  - In vivo study\* confirmed systemic bioavailability with single facial application of 500 mg of 1% kojic acid cream in 6 healthy postmenopausal women:
    - Mean  $C_{max}$  of 1.54 ng/ml
    - Mean  $AUC_{0-24\text{ h}}$  of 19.4 ng/ml x hr
- European Scientific Committee on Consumer Safety on kojic acid:
  - Safe at 1% as skin whitening agent to face and hands

\*2008 European Commission Scientific Committee on Consumer Products (SCCP): Opinion on Kojic Acid



# Human Safety (3)

- Availability of alternative approved therapies
  - Melasma
    - Fluocinolone acetonide, hydroquinone, and tretinoin cream, 0.01%/4%/0.05% (Tri-Luma)
  - Indications relating to iron chelation by kojic acid
    - For wound healing: Regranex Gel (a biologic product), cleared devices, grafts, and dressings
    - For photodamage prevention: No approved products

# Human Safety (4)

- Summary
  - Available data suggest that topical use of kojic acid in hyperpigmentation disorders may be associated with local irritancy
    - Reported adverse reactions transient and manageable
    - Allergic contact dermatitis reported
    - No reports of systemic adverse reactions
  - However, safety data on kojic acid use as a single active agent in treatment of hyperpigmentation disorders is limited
  - No clinical data for use of kojic acid in wound healing, including data on systemic exposure or use in open wounds; No published reports of the clinical use of kojic acid for the prevention of photodamage

# Effectiveness

- Hyperpigmentation disorders
  - Limited information of kojic acid in the topical treatment of hyperpigmentation disorders
  - Most clinical trials involve study in melasma and use of kojic acid in combination with other active ingredients but without adequate design to demonstrate contribution of kojic acid to efficacy

## Effectiveness (2)

- Hyperpigmentation disorders
  - Lim (1999) evaluated 40 Chinese women with epidermal melasma in a double-blind, randomized, within-subject, 12-week trial comparing
    - hydroquinone 2% and glycolic acid 10% gel; and
    - hydroquinone 2% and glycolic acid 10%, kojic acid 2% gel
  - Difference in clearance of melasma was not statistically significant between treatments (2 out of 40 with the gel containing kojic acid and 0 out of 40 with the gel not containing kojic acid;  $p = 0.9$ )

# Effectiveness (3)

- Hyperpigmentation disorders
  - Deo et al., (2013) conducted a 12-week, randomized, single-blind, parallel group trial of 80 adults with melasma comparing:
    - A – kojic acid 1% cream;
    - B – kojic acid 1%, hydroquinone 2% cream;
    - C – kojic acid 1%, betamethasone valerate 0.1% cream; and
    - D – kojic acid 1%, hydroquinone 2%, betamethasone valerate 0.1% cream
  - Information on the rate of clearance of melasma in the study subjects was not given, while reduction of MASI\* score was achieved in the following percentages of subjects:
 

Group A	Group B	Group C	Group D
59%	72%	54%	36%
  - The study design lacks key treatment arms to demonstrate a contribution of kojic acid to the treatment effect

\*MASI: melasma area and severity index

# Effectiveness (4)

- Hyperpigmentation disorders
  - Garcia et al., (1996) conducted a 12-week, randomized, active-controlled, bilateral comparison (split-face) trial in 38 subjects with melasma comparing:
    - kojic acid 2% and glycolic acid 5% gel; and
    - hydroquinone 2% and glycolic acid 5% gel
  - Clearance rates for melasma were not provided while reduction in hyperpigmentation showed the following percentages ( $p > 0.05$ ):

Equal on both sides	Greater with hydroquinone	Greater with kojic acid
51%	21%	28%

- Efficacy of kojic acid 2% in combination with glycolic acid 5% as gel formulation not established, as clearance rates for melasma are unknown for this study

# Effectiveness (5)



- Iron Chelation Uses
  - Wound healing and photodamage prevention
    - No published human clinical experience to support use of kojic acid in wound healing or prevention of skin photodamage
    - One published study of kojic acid use in rats as iron chelator for wound healing: deferiprone superior to kojic acid, which was not better than vehicle
    - One published study of kojic acid use in hairless mice as iron chelator for photodamage prevention: kojic acid prevented wrinkling from solar-simulated UV irradiation for 20 weeks

# Effectiveness (6)



- Seriousness of the conditions for proposed use of kojic acid
  - Hyperpigmentation disorders and photodamaged skin are not serious conditions *per se*, but pathological changes predisposing to skin cancer may be associated with photodamage
  - Wounds can be serious conditions depending on the location, size, depth, concomitant fluid/electrolyte loss, vascular supply, free radicals, wound infection, etc.



# Effectiveness (7)



- Summary
  - Most clinical trials assessing treatment of melasma included use of kojic acid in combination with other drug substances
  - Insufficient quality data from clinical trials to assess whether kojic acid aids in treatment of hyperpigmentation
  - No clinical data supporting effectiveness in wound healing or prevention of photodamage

# Historical Use in Compounding



- Kojic acid has been used, often in combination with other substances, in pharmacy compounding in the U.S. for decades
  - Uses: melasma and other hyperpigmentation disorders
- Extent of use cannot be precisely determined
  - Kojic acid products regulated in Japan as “quasi-drugs”
- Not found in the US Pharmacopeia or European, British or Japanese Pharmacopeias

# Recommendation



A balancing of the four evaluation criteria weighs **against** kojic acid being added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act

# Diindolymethane

## Pharmacy Compounding Advisory Committee Meeting November 3, 2016

Michael Brave, MD

Clinical Reviewer

Division of Oncology Products 1

Office of Hematology & Oncology Products

# Diindolylmethane Review Team



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**Ramesh Sood, PhD**, Senior Scientific Director (Acting), OPQ

# Nomination

- Diindolylmethane (DIM) has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Food, Drug, and Cosmetic Act (FD&C Act) “for use in the treatment for cancer”
- Nominated administration: 100 mg oral capsules



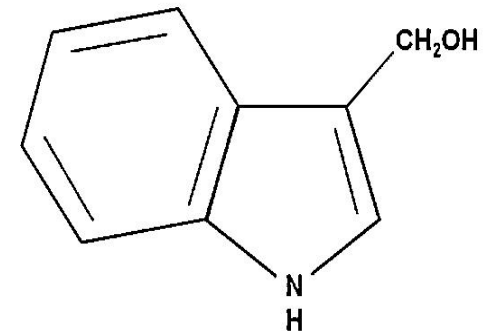
# Background

- DIM is an active metabolite of I3C, a phytochemical found in cruciferous vegetables (e.g., broccoli, cauliflower, kale, cabbage, Brussels sprouts, etc.)
- Epidemiological studies suggest that persons who regularly eat cruciferous vegetables have lower risks of some cancers
- DIM is currently available as a dietary ingredient in dietary supplements

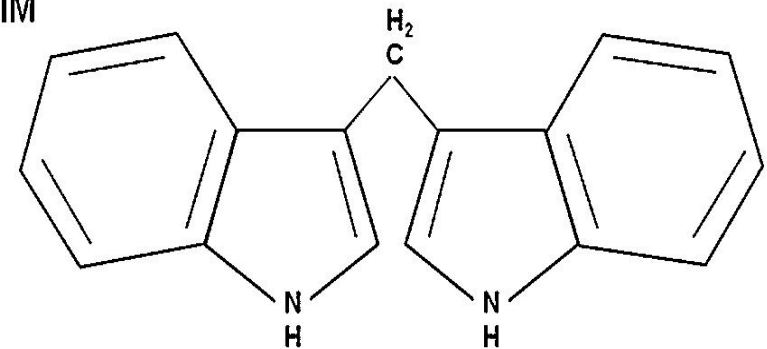
# Physical and Chemical Characterization

- Small organic molecule
- Indole-3-carbinol (I3C) is precursor of DIM
- DIM is the major biologically active form

I3C

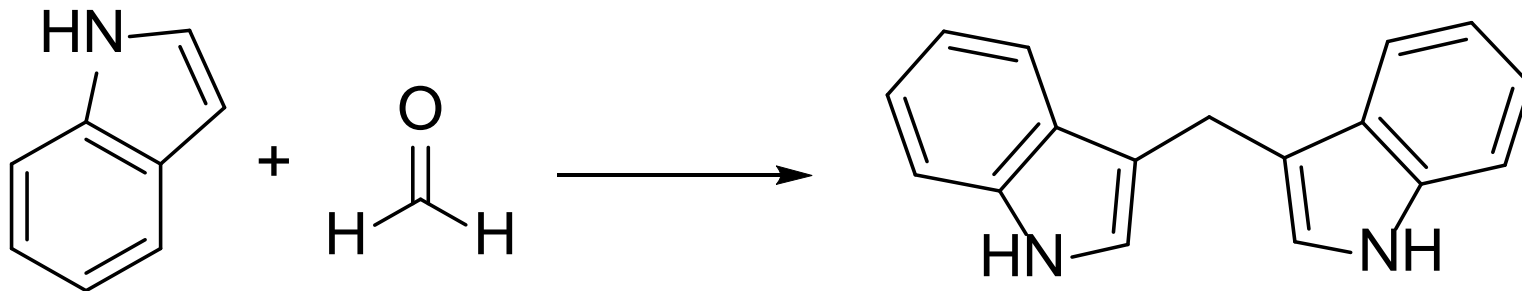


DIM





# Physical and Chemical Characterization (2)



- DIM is the condensation product of indole and formaldehyde
- Easily characterized by spectroscopy
- Impurities may include residual starting materials such as indole and formaldehyde
- Stable as solid when kept away from light and at 4°C

# Physical and Chemical Characterization (3)



- Summary
  - Based on the available information, there are no concerns about the physical and chemical characterization of DIM
    - Small organic molecule, active metabolite of I3C, found in cruciferous vegetables
    - Easily characterized by spectroscopy
    - Stable as a solid under ordinary storage conditions when kept away from light

# Pharmacology and Toxicology



- Mechanistic in vitro studies were conducted in a number of animal and human cancer cell lines. These point to potential anticancer mechanisms for DIM:
  - cell cycle arrest
  - increased incidence of apoptosis
  - modulation of estrogen metabolism
- Limited animal toxicology data
  - induced hepatic enzymes
  - potential for impact on the immune system
  - no information available on developmental and reproductive toxicity, mutagenicity, carcinogenicity, or toxicokinetics

# Pharmacology and Toxicology (2)



- Summary

- Based on data available in public databases, the available toxicology data indicate a potential safety concern
- Both the potential safety concerns and the overall limited amount of available data raise concerns about the use of DIM in compounding under section 503A of the FD&C Act

# Human Safety

- Published reports and clinical trials
  - Primarily minor, reversible gastrointestinal symptoms
  - Several serious events without substantive causal evidence
  - Safety and efficacy data from the published trials
- FDA Adverse Events Reporting System (FAERS)
  - 2 reports of altered mental status with insufficient data to assess causality
- CFSAN Adverse Events Reporting System (CAERS)
  - 18 reports from use as dietary supplement but limited data are available

# Human Safety

## Published Clinical Trials with I3C or DIM



- Studies reported in
  - Healthy volunteers
  - Women with abnormal cervical cytology
  - Women at risk for breast cancer
  - Men with prostate disease

# Human Safety

## Published Clinical Trials



### I3C or DIM in Healthy Volunteers

Author	Population	Treatment	Findings
Reed	Healthy females (n = 24)	I3C 400-1200 mg/day x 4 wk	<ul style="list-style-type: none"><li>• Plasma I3C undetectable</li><li>• DIM detected in plasma after single dose</li><li>• ↑ urinary 2OHE<sub>1</sub>:16aOHE<sub>1</sub></li><li>• GI distress dose limiting</li></ul>
Reed	Healthy volunteers (n = 24)	Bioresponse DIM 50- 300 mg single dose	<ul style="list-style-type: none"><li>• DIM detected in plasma after single dose</li><li>• GI distress dose limiting</li></ul>

Reed, Cancer Epidemiol Biomarkers Prev 2006;15:2477

Reed, Cancer Epidemiol Biomarkers Prev 2008;17:2619

# Human Safety

## Published Clinical Trials (2)



### I3C or DIM in Women with Abnormal Cervical Cytology

Author	Population	Treatment	Findings
Bell	Cervical interstitial neoplasia (n = 30)	I3C 200 or 400 mg/day v placebo x 12 wk	<ul style="list-style-type: none"> <li>• ↑ urinary 2OHE<sub>1</sub>:16aOHE<sub>1</sub></li> <li>• CIN regressed at 12 weeks in 8 of 17 I3C patients</li> </ul>
Del Priore	Cervical interstitial neoplasia (n = 64)	Bioresponse DIM 2 mg/kg/day v placebo x 3 months	<ul style="list-style-type: none"> <li>• No SAEs reported</li> <li>• No observed effect on cervical cytology</li> </ul>
Castañon	Cervical interstitial neoplasia (n = 551)	Bioresponse DIM 150 mg/kg v placebo x 3 months	<ul style="list-style-type: none"> <li>• No SAEs reported</li> <li>• No observed effect on cervical cytology</li> </ul>

Castañon, Br J Cancer 2012;106:45

Del Priore, Gynecol Oncol 2010;116:464

Bell, Gynecol Oncol, 2000;78:123



# Human Safety

## Published Clinical Trials (3)



### DIM in Women at Risk for Breast Cancer

Author	Population	Treatment	Findings
Dalessandri	Postmenop women with early breast cancer (n = 19)	Bioresponse DIM 108 mg/day v placebo x 30 days	↑ urinary 2OHE <sub>1</sub> :16aOHE <sub>1</sub>
Kotsopoulos	Women with BRCA1 mutation (n = 18)	Bioresponse DIM 300 mg/day v placebo x 4-6 wk	↑ BRCA1 mRNA expression
Nikitina	Women with BRCA1 mutation (n = 20)	Bioresponse DIM 300 mg/day v placebo x 4-6 wk	No observed effect on urinary 2OHE <sub>1</sub> :16aOHE <sub>1</sub>

Dalessandri, Nutrit Cancer 50;2:161

Kotsopoulos, Br J Cancer 2014;111:1269

Nikitina, Fam Cancer 2015;14:281

# Human Safety

## Published Clinical Trials (4)



### IC3 or DIM in Men with Prostate Disease

Author	Population	Treatment	Findings
Paltzev	Prostatic intraepithelial neoplasia (n = 21)	Infemin DIM 900 mg/day v placebo x 3 mo	PIN regressed
Heath (1)	Early stage prostate cancer (n = 36)	Bioresponse DIM 225 mg/day x 14 days pre-prostatectomy	↓ androgen receptor expression in prostate
Gee	Early stage prostate cancer (n = 45)	Bioresponse <sup>®</sup> DIM 900 mg/day v placebo x 3 mo	↑ urinary 2OHE <sub>1</sub> :16aOHE <sub>1</sub>
Heath (2)	Castrate-resistant, nonmetastatic prostate cancer (n = 12)	Infemin DIM 75-300 mg BID	Exposure dose proportional; MTD 225 mg BID

Paltzev, EPMA J 2016;7:5

Gee, Eur J Cancer Prev 2016;25:312

Heath (1), J Clin Oncol 2012;30suppl:abstr 1560

Heath (2), Am J Transl Res 2010;2:402

# Human Safety



- Summary
  - GI symptoms are dose limiting
  - Available data from published information and adverse event reporting do not establish causal link to serious adverse events

# Efficacy Summary



- Mechanistic studies may support rationale for development as a chemopreventive agent or as adjunct to chemotherapy
- No clinical trials have been identified that demonstrate a benefit of I3C or DIM in the treatment of cancer
- Cancer is a serious and life-threatening disease
- There are many approved therapies for the treatment of cancer

# Historical Use in Compounding



- Insufficient information available to determine how long DIM has been used in pharmacy compounding
  - Oral and topical compounded formulations are advertised on the internet
- Insufficient information from which to draw conclusions about extent of use
- DIM not found in foreign pharmacopeias

# Recommendation



- A balancing of the four evaluation criteria weighs **against** placing diindolymethane (DIM) on the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act

# Vasoactive Intestinal Peptide

**Pharmacy Compounding Advisory Committee Meeting  
November 3, 2016**

**Susan Johnson, Pharm.D., Ph.D.**

Associate Director

Office of Drug Evaluation IV

# Vasoactive Intestinal Peptide Review Team



**Susan Johnson, PharmD, PhD**, Associate Director, ODE IV

**Ben Zhang, PhD**, Chemistry Reviewer, OPQ

**Joseph Leginus, PhD**, Chemistry Reviewer, OPQ

**Craig Bertha, PhD**, Team Leader, OPQ

**Wafa Harrouk, PhD**, Pharmacology/Toxicology Reviewer, ODE IV

**Jennifer Shing, PhD**, Clinical Reviewer, ODE IV

**Elizabeth Marek, PharmD**, Historical Use Reviewer, OUDLC, OC

**Ramesh Sood, PhD**, Senior Scientific Advisor (Acting), OPQ

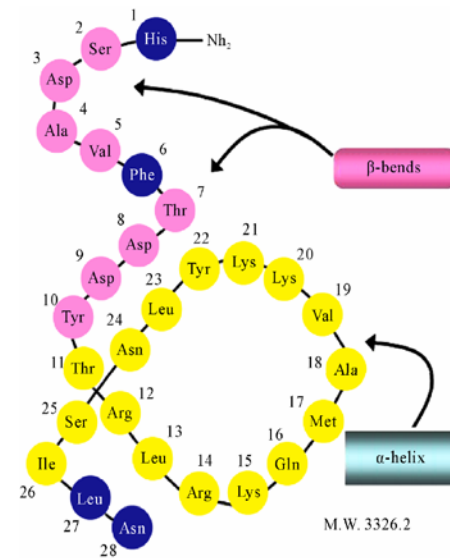
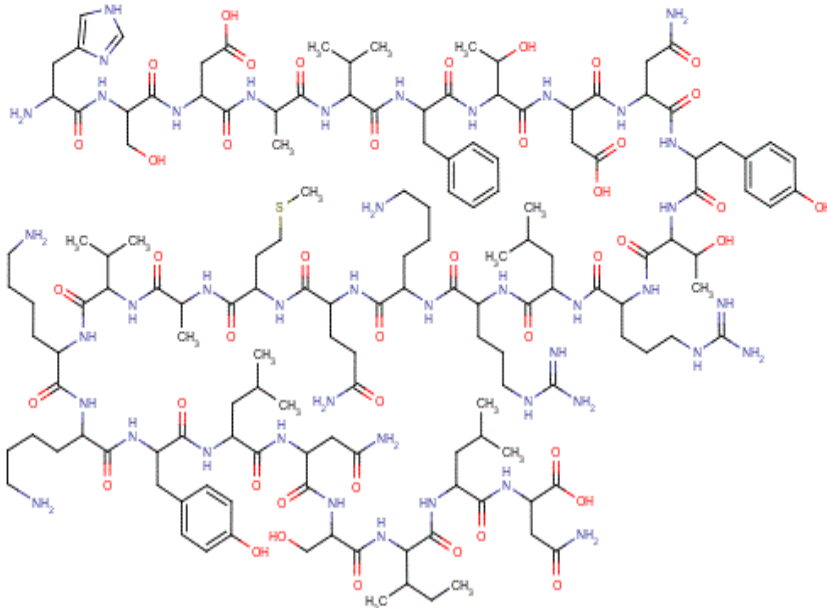


# Nomination

- Vasoactive intestinal peptide (VIP) has been nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for use as nasal spray in the treatment of a condition described as chronic inflammatory response syndrome (CIRS)

# Physical and Chemical Characterization

- Peptide hormone containing 28 amino acids residues
  - Secondary structure shows an  $\alpha$ -helix and two  $\beta$ -bends



(Igarashi et al, 2011)

# Physical and Chemical Characterization (2)



- VIP is prepared by solid phase peptide synthesis followed by purification by HPLC
- An appropriate bioassay can confirm the proper secondary structure of VIP
- Stability of the VIP in aqueous solution depends upon the pH and storage temperature:
  - Very dilute solutions are prone to degradation and potential aggregate formation, which may increase the potential for immunogenicity
  - The stability of the compounded product for nasal spray would depend upon maintaining proper solution pH and storage temperature of the solution

# Physical and Chemical Characterization (3)



- Impurities from the manufacturing process may include:
  - Modifications of the peptide such as deletion or insertion sequences, diastereomers, modified functional groups
  - Residual solvents and reagents (e.g., dimethylformamide DMF), acetonitrile
- Impurities from degradation may include:
  - Aggregates
  - Changes to the structural integrity (secondary structure) of the peptide potentially related to leachables from nasal spray container
  - Peptide fragments

# Physical and Chemical Characterization (4)



- Nasal Drug Delivery
  - Safety and efficacy of VIP can be affected by nasal delivery from a nasal spray as a result of its physical and chemical characteristics
  - The bioavailability of the peptide may be impacted by the physiological factors that can affect intranasal delivery, such as:
    - Nasal membrane permeability
    - Mucociliary clearance
    - Enzymatic degradation
  - Note: accurate and consistent administration of an API via a nasal spray depends on multiple factors (e.g., droplet size distribution, plume geometry, priming requirements)

# Physical and Chemical Characterization (5)



- Summary

- VIP is a 28 amino acid peptide hormone prepared by solid-phase peptide synthesis
- Bioassay may be useful to confirm the proper secondary structure of the formulated bulk substance
- Solution stability depends upon pH and storage temperature
- Very dilute solutions are prone to degradation and potential aggregate formation, which may increase potential immunogenicity
- Accurate delivery of VIP will be dependent on the complex factors associated with the used nasal spray device

# Safety

- General

- Pharmacology

- In humans and animals, VIP is an endogenous neuropeptide found in multiple organs and cell types
    - Diverse physiologic roles
      - regulation of blood flow
      - smooth muscle relaxation
      - stimulation of exocrine secretion

- Pharmacokinetics

- Short systemic half-life
    - Rapid hepatic clearance
    - Crosses blood brain barrier

# Safety (2)



- Nonclinical

- Acute Toxicity, Genotoxicity, Developmental and Reproductive Toxicity and Toxicokinetics
  - No data available
- Repeat Dose Toxicity
  - VIP administered intranasally to Parkinson's mouse model showed improvement in brain function (spatial learning & memory performance)
  - VIP administered subcutaneously using a carrier molecule for up to 8 weeks showed a longer half life. No data on toxicity endpoints were captured
- Carcinogenicity
  - A 45 week tumor promotion assay was conducted in rats; VIP was found to be a colon cancer promotor
  - No traditional 2-year carcinogenicity study has been conducted with VIP alone



# Safety (3)

- Clinical

- Immunologic responses to peptide variations should be anticipated
  - VIP, peptide impurities and degradants
  - Peptides present in formulation need to be characterized at the time of synthesis and controlled throughout the product's shelf life
- Adverse events from clinical trials
  - Adverse events in multiple exploratory efficacy trials have been mild; apparently related to VIP's vasoactive effects
  - However, a study of orally inhaled VIP on pulmonary arterial hypertension reported "a group of patients" with (Galie et al., 2012)
    - Increase in VIP auto-antibodies
    - Two cases were **severe**
- No reports from FDA Adverse Events Reporting System (FAERS) or CFSAN Adverse Events Reporting System (CAERS)

# Safety (4)



- **Summary**

- The available nonclinical data are inadequate to characterize the safety of VIP, particularly for chronic use
- In clinical studies, the majority of adverse events have been mild and apparently related to VIP pharmacology as a vasoactive agent
- Severe immunologic reactions have been reported
- Characterization and control of peptide impurities and degradants is necessary for safe use of VIP
- There are no products approved in the United States for the treatment of CIRS

# Effectiveness



- Nominated for use in the treatment of Chronic Inflammatory Response Syndrome (CIRS)
- CIRS does not appear in standard disease indexes
  - International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> revision (ICD-10)
  - Medical Dictionary for Regulatory Activities (MedDRA)
- One publication reports the study of VIP in the treatment of CIRS. This is for a condition in which CIRS is proposed to be attributable to exposure to water damaged buildings (WDB), CIRS-WDB

# Effectiveness (2)

- Study of VIP in CIRS

- N = 20; enrollment based on:

- Reported exposure to a WDB
- Patients were reported to have failed prior treatments for CIRS
- Entry criteria for identity and severity of symptoms, and plasma levels of monitored substances were not specified

- Intranasal spray administration of 50 mcg VIP QID for 18 months

- 8 of 20 patients were reported to have used VIP TID or QID; others used VIP less frequently

- Evaluations at baseline, 12 and 18 months

- Levels of 12 endogenous chemicals were assessed, including VIP
- No primary endpoints were identified among these and no efficacy thresholds were specified
- Timing of VIP sampling relative to dosing was not specified
- At 18 months, mean VIP was reported to be statistically lower than controls

# Effectiveness (3)



- Summary
  - Inadequate clinical information regarding condition for which VIP's use has been nominated (CIRS)
  - The single trial of the use of VIP to treat CIRS-WDB does not provide a basis to conclude that VIP is associated with clinical improvement
  - Neither nonclinical nor clinical data establish that intranasal delivery of VIP results in systemic exposure

# Historical Use in Compounding



- There is insufficient information available to determine how long VIP has been used in pharmacy compounding
- Nasal and injectable compounded formulations of VIP are advertised on the internet by US pharmacies
- Aviptadil (alternate name of VIP) has been approved in New Zealand, Denmark, and the United Kingdom, in combination with phentolamine, for intracavernosal injection for the symptomatic treatment of erectile dysfunction in adult men
- VIP and Aviptadil were not found in foreign pharmacopeias

# Recommendation



A balancing of the evaluation criteria *weighs against* placing VIP on the list of bulk drug substances that can be used to compound drug products in accordance with 503A of the FD&C Act

# Drug Products that Employ Transdermal or Topical Delivery Systems (TDS)\*

Caroline Strasinger, PhD

Office of New Drug Product

Office of Pharmaceutical Quality

Center for Drug Evaluation and Research

\* This presentation does not consider liquids and semi-solids such as gels, creams, lotions, foams, ointments and sprays.



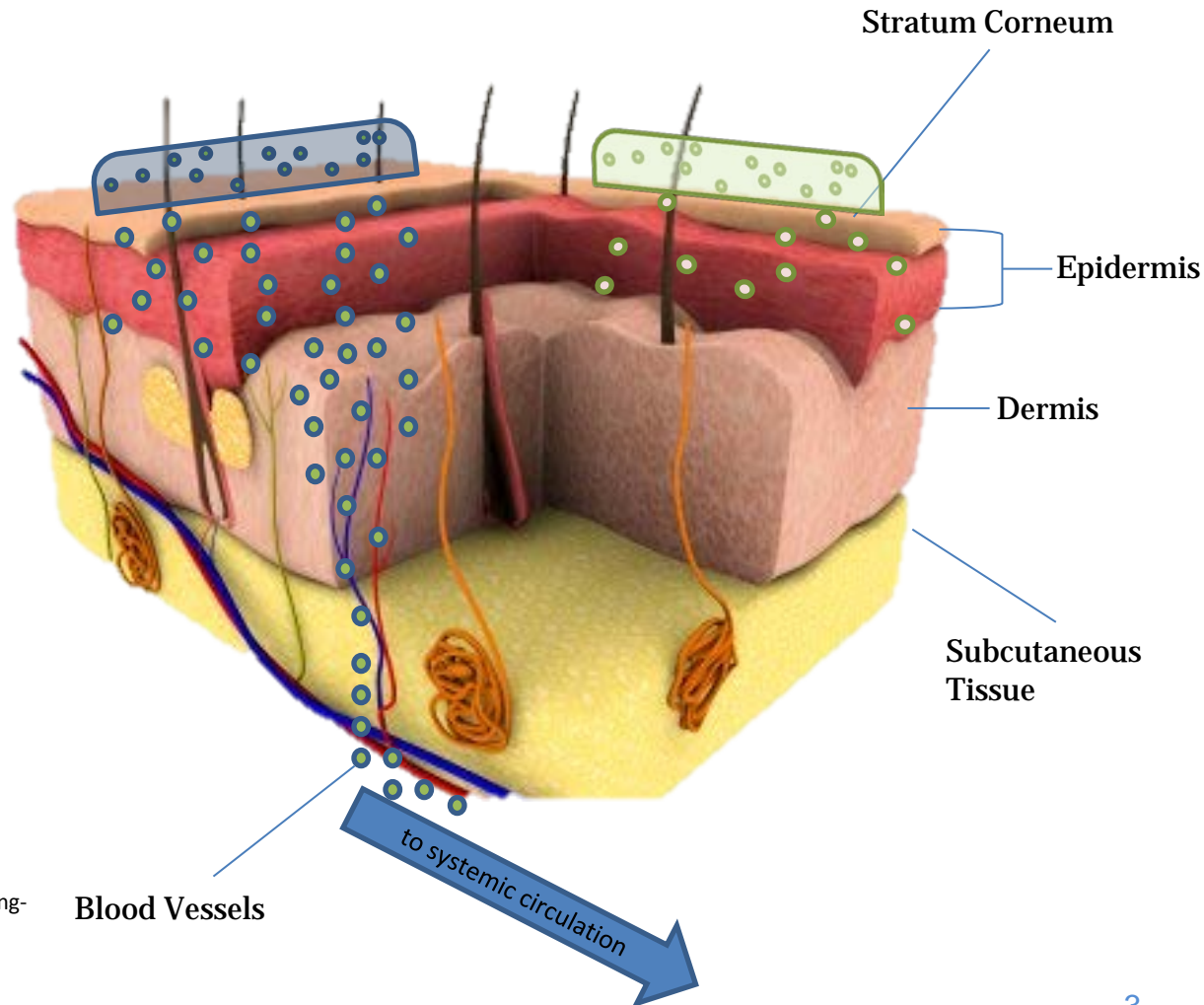
# Overview of Presentation

- Drug Products that Employ Transdermal or Topical Delivery Systems (TDS) Background
- Evaluation Criteria for TDS
  - Complex formulation
  - Complex drug delivery mechanism
  - Complex dosage form
  - Complex characterization and control of drug bioavailability
  - Complex compounding process
  - Complex physicochemical or analytical testing
- Recommendation

# TDS Background



- Transdermal delivery systems are designed to deliver active ingredient across the skin and into systemic circulation
- Topical delivery systems are designed to deliver the active ingredient into local tissue



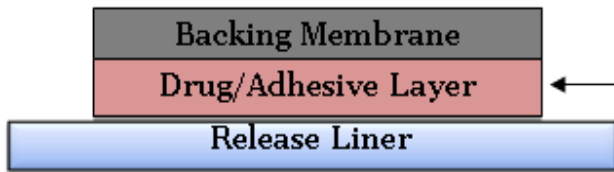
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## TDS Background (2)

- Drug products that employ either transdermal or topical delivery systems present similar manufacturing and quality control concerns which may lead to patient safety risks
- The Agency did not evaluate liquids and semi-solids such as gels, creams, lotions, foams, ointments and sprays in its review

# TDS Background (3)

## Matrix Type TDS



May also contain many other excipients, and/or may include more complex designs

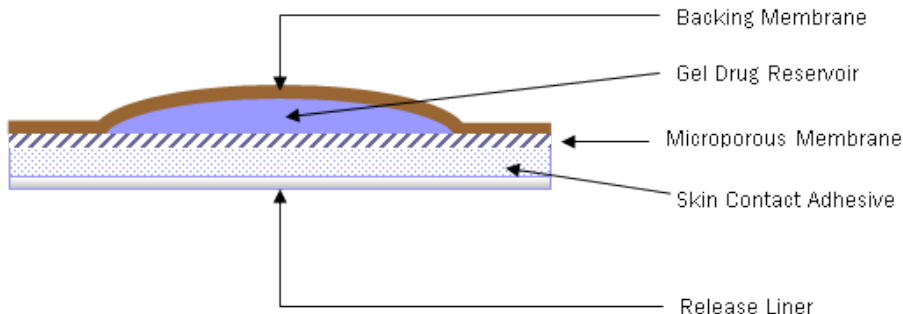
## Commercial Examples

Nicotine Transdermal System  
Lidocaine 5%



[https://www.nicodermcq.com/content/dam/global/CF\\_ConsumerHealthcare/cf-wellness-quit/en\\_us/Nicodermcq/Home\\_page/new\\_updates/Pod\\_4.jpg](https://www.nicodermcq.com/content/dam/global/CF_ConsumerHealthcare/cf-wellness-quit/en_us/Nicodermcq/Home_page/new_updates/Pod_4.jpg)

## Reservoir Type TDS

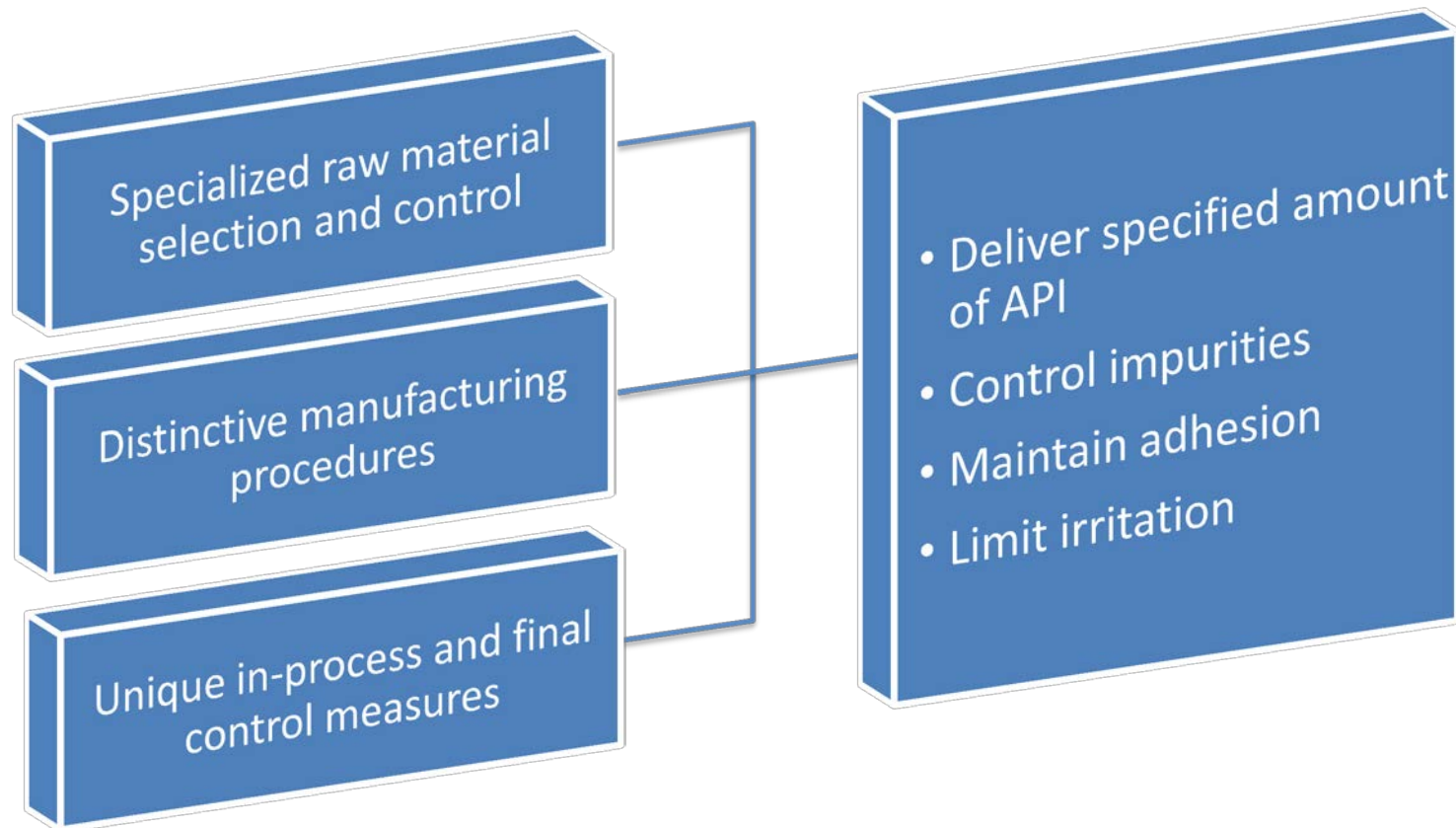


## Testosterone Transdermal System



# TDS Background (4)

TDS Characteristics → Quality Product



# TDS Have Complex Formulations



- API delivery through the skin is influenced by:
  - Complex characteristics of the active ingredient(s) and other excipients
  - Batch-to-batch variability in the active ingredient(s) and excipients
- These factors make it difficult to maintain adequate functional properties of adhesion and minimal irritation

# TDS Have Complex Formulations (2)



- Properties of API that impact product performance
  - Polymorphic form
    - Inadequate control may lead to excessive crystallization in the vehicle (adhesive matrix or reservoir)
  - Solubility
    - Dissolved state and sink conditions necessary for delivery across the skin
    - Solubility in the vehicle may vary due to vast array of excipients
  - Compatibility
    - Physical, chemical, or physiological interactions between API and excipients may impact product stability, manufacturability, efficacy, performance, therapeutic activity, and can lead to varying side effect profiles
  - Purity
    - Skin permeability of impurities, such as degradants, are rarely known

# TDS Have Complex Formulations (3)



- Characterization and control of key functional excipients are critical to safety, efficacy, and quality of the TDS
- Excipients used in TDS can include various and multiple adhesives, permeation enhancers, rate controlling or non-rate controlling membranes, solubilizers, plasticizers, or tackifiers
- All excipients and their varying combinations can influence active ingredient delivery or product adhesion, and therefore the safety profile



# TDS Have Complex Formulations (4)



- Adhesives
  - Performance of a finished product can vary widely based on the selected adhesive system
  - There are primarily three types of adhesives used in TDS (acrylate, Polyisobutylene/Polybutene, and silicone) however hundreds of different grades of each exist
    - Each grade with individualized raw material characteristics (e.g., viscosity profiles, impurity profiles, solvent systems, molecular weight ratios, selected cross linkers, functional end groups)
  - Adhesives are qualified through extensive testing as a raw material, as a laminate (in the absence of API and other excipients) and in the final product

# TDS Have Complex Formulations (5)



- TDS are created from ingredients with highly variable chemical and physical properties
- TDS need predictable and controllable composition and stability and exhibit consistent functionality all of which can be influenced by raw material selected and how they are controlled

Complexity of TDS formulations presents demonstrable difficulties for compounding

# TDS Have a Complex Delivery Mechanism



- Factors influencing the delivery of API through the skin

## Quantitative and Qualitative Composition

- Proper excipient selection
- Excipients will individually and collectively influence the rate of delivery and product performance

## Function

- Ability to adhere for the duration of wear

## Physical Design

- Surface area
- Backing membrane
- Thickness of matrix

# TDS Have a Complex Delivery Mechanism (2)



- API delivery is proportional to the surface area of TDS in contact with skin
- Thickness of the adhesive matrix and type of backing membrane can influence delivery and adhesion of TDS
  - Low Moisture Vapor Transmission Ratio backing membranes provide occlusion and thus increase the stratum corneum hydration and skin permeability
  - Stiffness of backing membrane, thickness of adhesive layer and surface area of product can influence skin adhesion

# TDS Have a Complex Delivery Mechanism (3)

- The mechanism by which an active ingredient is delivered through the skin is complex because:
  - It involves designing and manufacturing a product that can deliver a specific amount of API per unit area per unit time, maintain adhesion for the duration of intended wear, and have minimal irritation of the skin throughout wear and upon removal
  - The dose delivered is affected by several factors which may adversely affect safety and efficacy including
    - Lack of precise control of raw materials
    - Manufacturing process

Complexity of this drug delivery mechanism presents a demonstrable difficulty for compounding

# TDS are Complex Dosage Forms

- As already explained, TDS have complex formulations and complex drug delivery mechanisms
- TDS necessitate:
  - Extensive product development
  - Characterization and precise selection control over the raw materials and the manufacturing process
- This is essential for evaluating the drug delivery and performance characteristics of TDS

TDS are complex dosage forms that present a demonstrable difficulty for compounding

# Bioavailability of TDS is Difficult to Characterize and Control



- TDS are complex and even small changes in performance characteristics can have a significant impact on local and systemic bioavailability and efficacy of the product
- Locally Acting (Topical Delivery Systems)
  - May have little to no systemic uptake
    - Bioavailability is assessed via pharmacodynamic studies or clinical endpoint approaches
- Systemically Acting (Transdermal Delivery Systems)
  - Physiological factors affect bioavailability of the active ingredient
    - Skin depot (layers of skin can serve as a reservoir)
    - Absorption differences at different application sites

# Bioavailability of TDS is Difficult to Characterize and Control (2)



- To assess bioavailability as part of the approval process, Applicants typically perform a multitude of in vitro, pharmacokinetic, and other in vivo assessments
- There is no single, easily reproducible, reliable method of measurement that can quantitate the dose delivered by the product and received by the patient
  - These measurements would be necessary to consistently make product with a delivered dose that uniformly falls within an acceptable range
  - Because there are no simple methods to characterize bioavailability, compounded TDS may not possess the appropriate bioavailability profile and thus could pose significant safety and efficacy risks to the patient



# Bioavailability of TDS is Difficult to Characterize and Control (3)



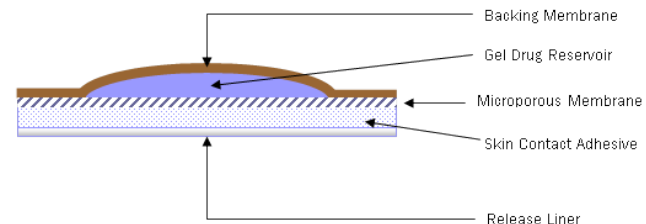
- In vitro assessments (in vitro release and in vitro adhesion testing) alone, are not sufficient to accurately predict permeation, bioavailability, and overall clinical effect
- Even small changes in performance characteristics can significantly impact the local and systemic bioavailability and efficacy of a product

TDS are complex systems for which bioavailability is difficult to assess and may not be achieved and therefore present a demonstrable difficulty for compounding

# TDS Involve Complex Compounding Processes

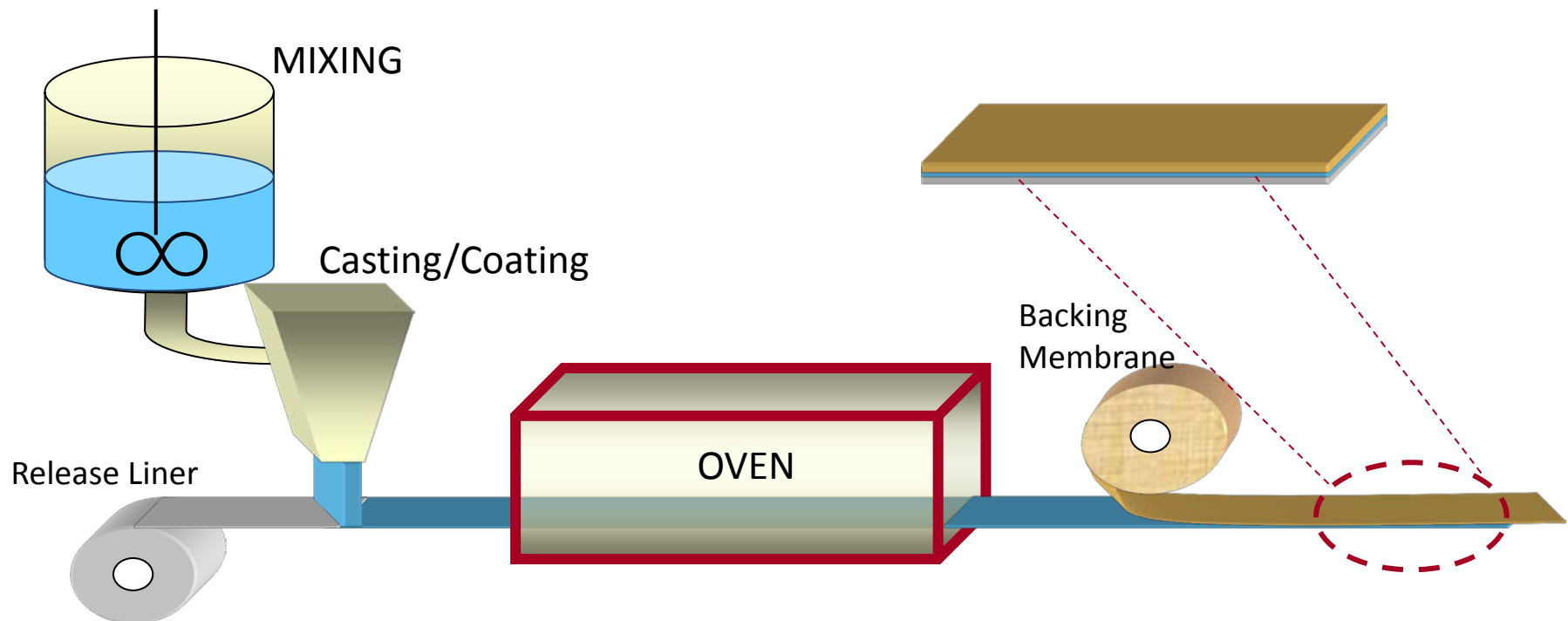


- TDS require specialized processing to reproducibly yield products with predictable drug delivery and functional parameters that are critical for product performance
- TDS employing reservoir type delivery systems need specialized heat sealing equipment to fully entrap the gel between the membrane layers of the product to prevent leaks



# TDS Involve Complex Compounding Processes (2)

The simplest of matrix products involve primarily three process (1) Mixing, (2) Casting, (3) Drying and Laminating



# TDS Involve Complex Compounding Processes (3)



- Mixing is critical to achieving a uniform mixture of API and excipients
  - Exceeding the solubility limit, incomplete mixing or dissolution of API can result in decreased API available for delivery
  - Over mixing or excessive propeller speeds can introduce air bubbles resulting in non-uniformity of cast film
- Formulations often contain immiscible adhesives or penetration enhancers to achieve desired delivery and maintain proper adhesion
  - Variable mixing times, holds, or transfers can lead to unintended phase separation

# TDS Involve Complex Compounding Processes (4)



- Casting is critical to achieving a uniform thickness or coat weight
  - Typically performed using automated equipment with precise gap thickness and speed controls to produce uniform thickness and coat weight
    - Varying thickness/coat weight directly affects total API content of the film
  - Numerous release liners are commercially available. Selecting a release liner that is incompatible with the mix or casting on the non-coated side of the release liner can result in permanent bonding of the release liner to the adhesive matrix rendering the product unusable

# TDS Involve Complex Compounding Processes (5)



- Appropriate drying is critical for driving off solvents
  - Conventionally performed in multi-chamber ovens with precise control of temperature, drying time, and airflow
    - Temperature profiles optimized to composition
      - Too high of temperature at the start can drive solvents off too quickly leading to bubbles
      - Too low or short of drying times may not drive off enough solvents, leaving behind a too soft or tacky TDS and impacting stability, delivery, and adhesion properties
  - Critical step for controlling residual solvents and volatile adhesive impurities
    - Drying processes used to reduce these solvents and impurities to acceptable levels
  - If the critical process parameters of drying temperature, dryer air flow, and line speed are not adequately optimized and controlled, efficacy, product performance, and safety may be negatively affected

# TDS Involve Complex Compounding Processes (6)

- Conclusion
  - The compounding processes for TDS are complex, and the use of specialized equipment allowing for automated processing and precise control are important for both reservoir and matrix type delivery systems
  - Any errors in the steps of mixing, casting, or drying of a TDS are reasonably likely to result in variability in the delivered dose, product performance inconsistency, and/or unsafe levels of impurities

Compounding TDS involves complex processes that present demonstrable difficulties

# TDS Necessitate Complex Testing



- Extensive characterization and developmental studies on the specific formulation, the functional properties, and the manufacturing process is necessary to help assure satisfactory performance
- A large number of complex tests are needed to help ensure satisfactory performance of TDS
  - Raw material testing
  - Release testing
  - Stability testing



# TDS Necessitate Complex Testing (2)



- Raw material testing
  - Rigorous qualification of key excipients
    - Raw material properties like viscosity and impurity content often affect the quality and safety attributes
    - Suppliers' adhesive specifications are often wide; thus the properties of the raw material vary greatly
      - Tighter internal acceptance specifications at the manufacturing site or independently conducting complex testing of raw materials needed

# TDS Necessitate Complex Testing (3)



- Release testing – in vitro adhesion testing
  - Typically includes peel adhesion, release liner peel, tack and shear
    - Characteristics of the method (conditioning times, angle of peel, peel rate or substrate) can significantly affect the results obtained
    - Complexity of testing increase with the number of operators, each of which would have to achieve the same results consistently
  - In vitro adhesion does not correlate well with in vivo adhesion
    - In vivo adhesion testing with the proposed TDS is performed during clinical development
    - Once the TDS has demonstrated adequate adhesion, in vitro tests are used to ensure the same product characteristics are maintained batch to batch and during shelf life
  - Due to the impact of and interplay among API, adhesives, and other excipients on adhesion properties, compounded TDS would need to be tested through in vivo and in vitro adhesion tests to establish consistent product performance

# TDS Necessitate Complex Testing (4)



- Release testing – other testing examples
  - Assay, uniformity, impurity, and residual solvent testing
    - Similar to in vitro adhesion testing, sophisticated equipment and specialized methods need to be developed
    - Developing a method that can first extract particular components (e.g. API), from a unique adhesive matrix and then quantify the active ingredient to the preciseness of 90-110% of the total drug load of the TDS is difficult
    - The lack of quantitation of residual monomers, adhesive impurities, and residual solvents would adversely affect the safety of the product in each batch manufactured

# TDS Necessitate Complex Testing (5)



- Stability testing
  - Quality concerns that can arise on stability
    - Cold flow – creep or oozing of the adhesive matrix beyond the perimeter of the backing membrane or through the release liner slit
      - Can lead to use and adhesion difficulties
    - Crystallization
      - Impact on delivery and adhesion
    - Leachables – chemical impurities from backing membrane, release liner or container closure that leach into the adhesive matrix or reservoir over time
      - Toxicity and skin penetration potential unknown
    - Volatile penetration enhancers
      - Concentration of enhancer must be maintained throughout storage or an impact on delivery can be expected

# TDS Necessitate Complex Testing (6)

- Conclusion
  - TDS require complex physicochemical and analytical testing (raw material, release, and stability) to help assure satisfactory performance
  - These tests are difficult to develop, validate, and perform routinely, use highly specialized and unique equipment, and analysts that have received considerable training

TDS requires complex testing that presents demonstrable difficulties for compounding

# Risk and Benefit to Patients

- Approximately 25 unique TDS on the market with many available generic formulations approved under NDAs and ANDAs
  - Pain management, contraception, Alzheimer's, smoking cessation, etc.
- As discussed, strict quality control on raw materials, the manufacturing process and the product are needed
- Some ingredients in approved TDS may cause hypersensitivity. However, an attempt to compound TDS by replacing or removing a specified ingredient is reasonably likely to adversely affect product performance

# Risk and Benefit to Patients (2)



## Most Common Excipients to Cause Irritation

<p><b>Active Ingredient</b></p> <ul style="list-style-type: none"><li>• Can not be avoided</li></ul>	<p><b>Adhesive</b></p> <ul style="list-style-type: none"><li>• Substitution or removal can change delivery and/or performance</li></ul>	<p><b>Penetration Enhancer</b></p> <ul style="list-style-type: none"><li>• Substitution or removal can change delivery and/or performance</li></ul>
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Any benefit of allowing these products to be compounded is outweighed by the risks discussed

# Recommendation

- TDS present demonstrable difficulties for compounding that reasonably demonstrate, and are reasonably like to lead to, an adverse effect on the safety or effectiveness of this category of drugs, taking into account the risks and benefits to patients
- Accordingly, we believe TDS should be included in the Difficult to Compound List under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act