



# L-Citrulline

**Pharmacy Compounding Advisory Committee Meeting  
November 20, 2017**

**Susan Johnson, PharmD, PhD**  
Associate Director  
Office of Drug Evaluation IV  
Office of New Drugs

## L-Citrulline Review Team



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**Elizabeth Hankla, PharmD**, Consumer Safety Officer, OUDLC, OC

## Nomination

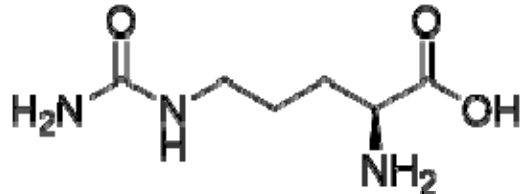


- L-citrulline has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug and Cosmetic Act (FD&C Act)
- It is proposed for oral use in the treatment of urea cycle disorders (UCDs)

# Physical and Chemical Characterization



- Non-essential amino acid, used in the human body in the L-form

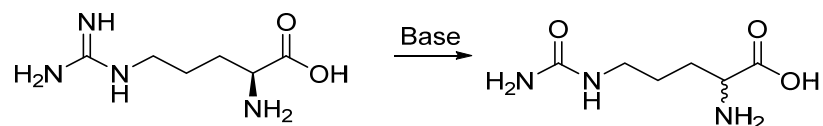


- Well characterized substance
- Soluble in water
- Likely to be stable under ordinary storage conditions as solid or liquid oral dosage forms

## Physical and Chemical Characterization (2)



- Possible synthetic routes
  - L-citrulline is mainly produced by fermentation of L-arginine as the substrate with special microorganisms such as the L-arginine auxotrophs *arthrobacterpa rafneus* and *Bacillus subtilis*.
  - L-citrulline can also be obtained through chemical synthesis. The synthetic route is shown in the scheme below. This route is much less efficient with harsh reaction conditions, tedious separation procedures, and environmentally unfriendly reagents.



### Conclusion:

- L-citrulline is well characterized
- It is likely to be stable under ordinary storage conditions as solid or liquid oral dosage forms

## Historical Use in Compounding



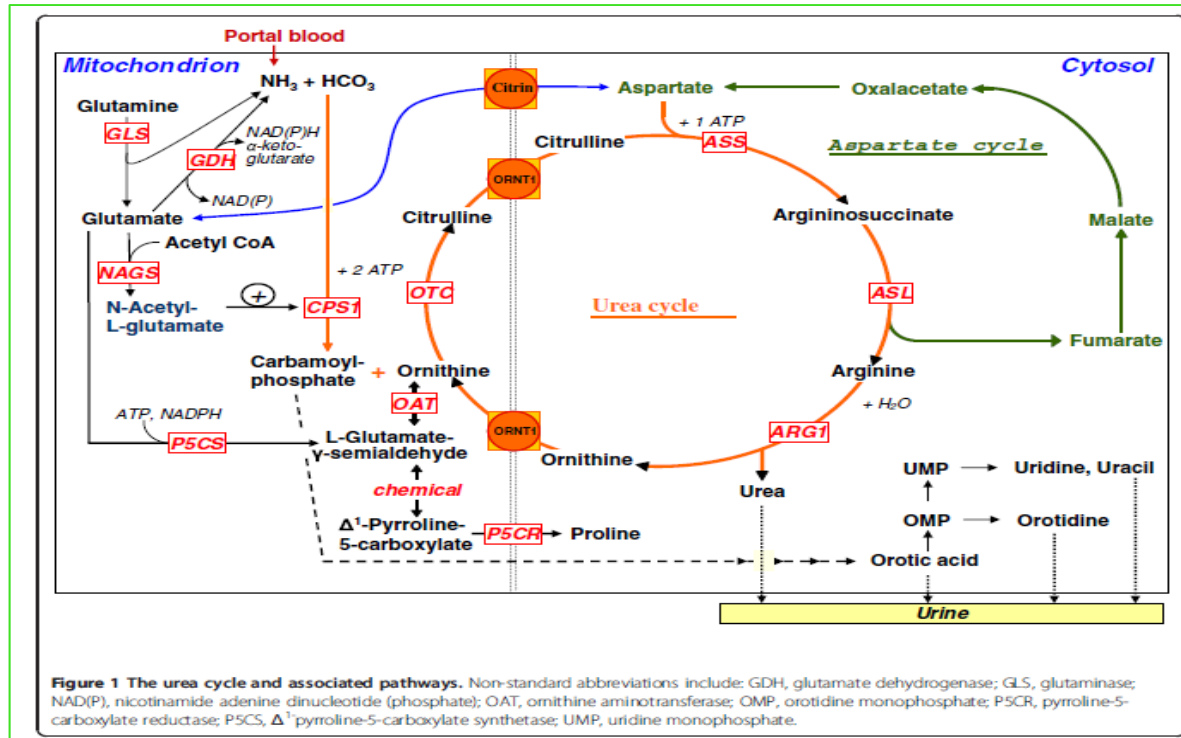
- Based on published literature, L-citrulline has been used clinically for the treatment of UCDs for at least 30 years
- Extent of use cannot be determined but practice guidelines recommend L-citrulline for therapy of certain UCDs
- L-citrulline is not listed in the British, European, or Japanese Pharmacopeias
- Currently available as a dietary ingredient in dietary supplement products

## General Pharmacology



- Non-essential amino acid
  - Found in foods such as cucumber, squash, pumpkins, and watermelon
- Synthesized in humans in the liver and intestine
- Intermediate in urea cycle
  - Basic function of urea cycle is to detoxify ammonia through conversion to urea
- L-citrulline has other functions - e.g., antioxidant and vasodilator

# Urea Cycle



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# Pharmacokinetics



- In sheep, a single intravenous dose of L-citrulline increased levels of L-citrulline and L-arginine in maternal and fetal plasma (between 5 and 60 min after dosing), suggesting L-citrulline can pass through the placenta to the fetus (Lassala et al., 2009)
- In healthy adults, oral dosing of 2 g to 15 g L-citrulline produced dose-dependent increases in AUC (Moinard 2008)
  - Mean C<sub>max</sub> of 15 g dose was 3849  $\mu\text{mol/L}$  (674 mg/L)
  - Mean AUC of 15 g dose was 8637  $\mu\text{mol}\cdot\text{h/L}$  (1513 mg/L)
  - Mean elimination half-life was 1 hour (not dose dependent)

# Nonclinical Safety



- Acute toxicity
  - Oral doses of citrulline malate (1.2 or 2.4 mg/kg) in male rats had no effect on rectal temperature, body weight, food consumption, or muscular performance (Verleye 1995)
- Repeat dose toxicity
  - Oral citrulline fed in rat diet for 6 days (10.1 g/kg) did not affect body weight or food consumption (Hartman 1994)
  - Puppies fed citrulline for 14 days (225 mg/kg/day), after receiving an arginine-free diet, experienced weight gain to near normal levels (Czarnecki and Baker 1984)
  - Kittens fed citrulline for 10 days (830 mg/kg/day) maintained normal growth rate while receiving an arginine-free diet (Morris 1979)
- No nonclinical safety data were found for L-citrulline with respect to:
  - Genotoxicity
  - Developmental and reproductive toxicity
  - Carcinogenicity

# Clinical Safety



- Adverse Events
  - FDA Adverse Event Reporting System (FAERS)
    - 15 unique reports of L-citrulline or L-citrulline preparations
    - 9 reports involved the recall of subpotent L-citrulline
    - Association of L-citrulline with the other 6 cases cannot be assessed due to lack of information
  - CFSAN Adverse Event Reporting System (CAERS)
    - Total of 332 reports
    - L-citrulline product included other herbs, vitamins, and/or amino acids
      - 3 deaths were reported; multiple serious reactions
      - Confounded by use of multiple supplements preventing causality assessment
  - No clinical trials to assess safety or efficacy; no AEs reported in pharmacokinetic studies
  - Published case reports of UCD patients developing hyperammonemia in association with use of L-citrulline product found to be sub-potent

## Safety Conclusion



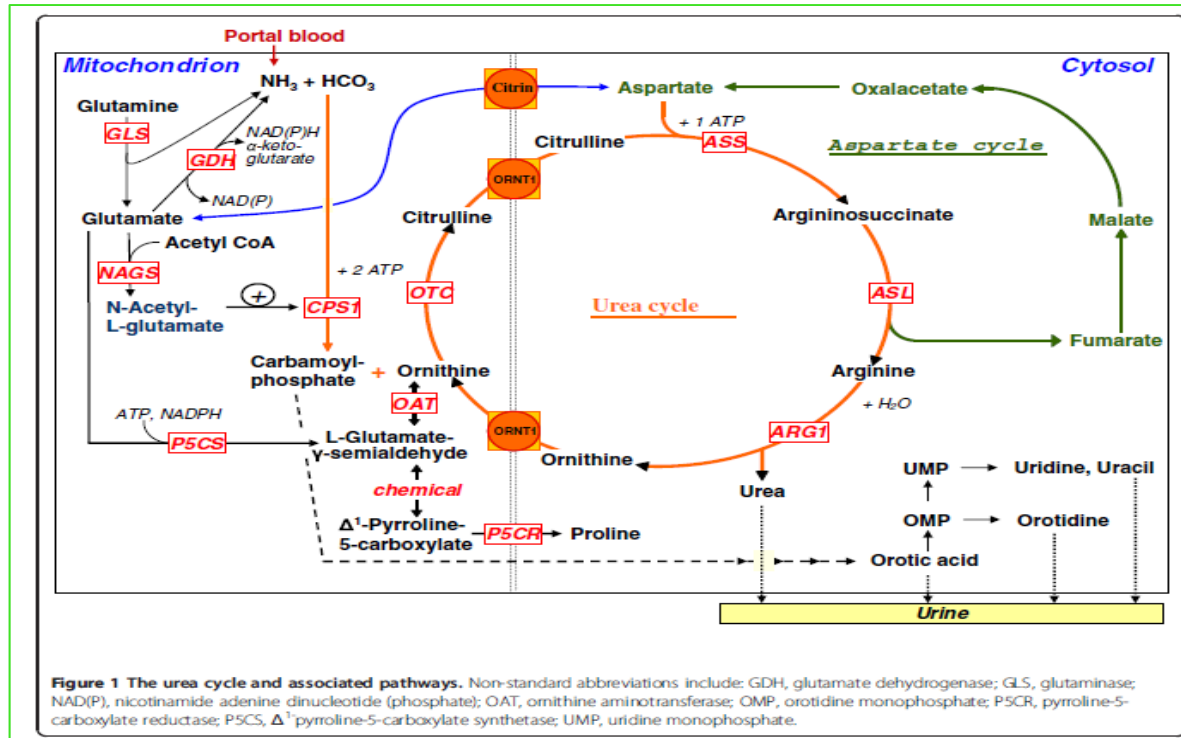
- Limited safety data available so safety issues can not be ruled out
- Adverse event data can not be evaluated for causality
- Decades of use has not been associated with safety concerns

# Efficacy



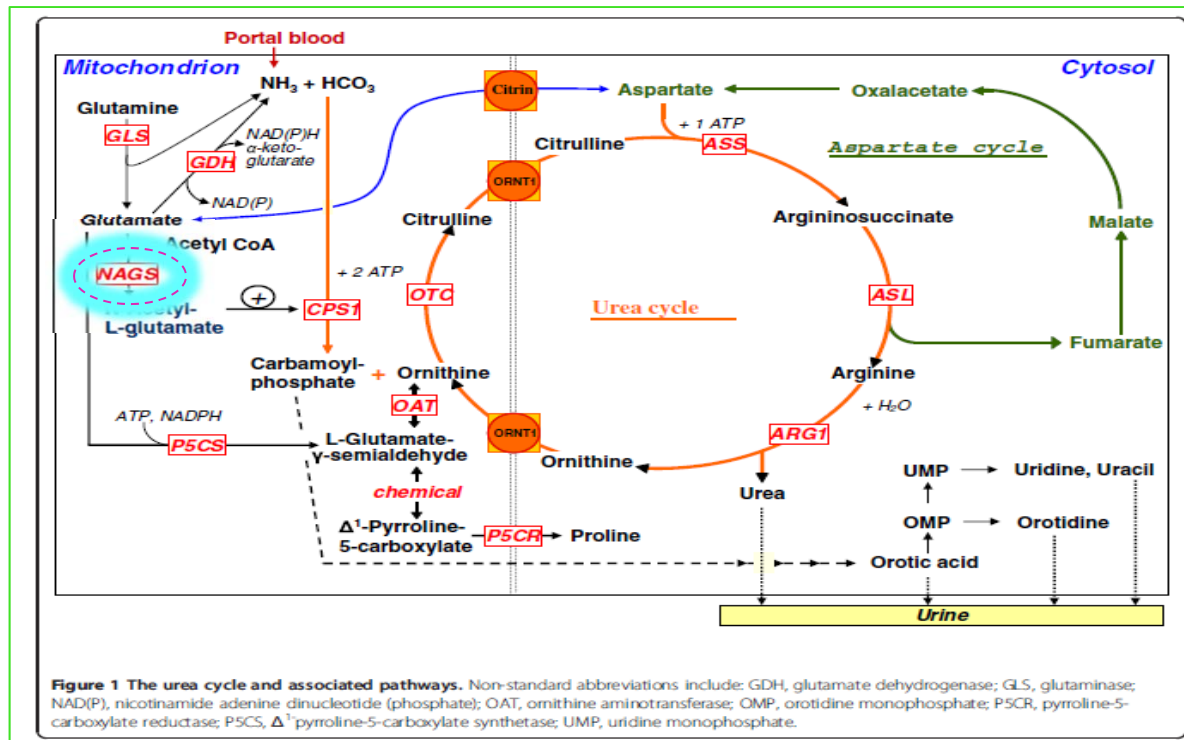
- Urea cycle disorders are rare diseases; predominantly genetic enzyme deficiencies
- Onset of UCDs
  - Neonatal - complete enzyme deficiency
  - Older children, adults - partial enzyme deficiency
- Hyperammonemia is the principle sign
  - Differential diagnosis is based on co-existing changes in plasma levels of amino acids, glucose, acid/base
  - Often accompanied by neurologic signs and symptoms
- FDA's efficacy assessment
  - N-Acetylglutamate Synthetase Deficiency (NAGSD)
  - Carbamyl Phosphate Synthetase 1 Deficiency (CPS1D)
  - Ornithine Transcarbamylase Deficiency (OTCD)
  - Ornithine Translocase Deficiency (HHH syndrome)

# Urea Cycle



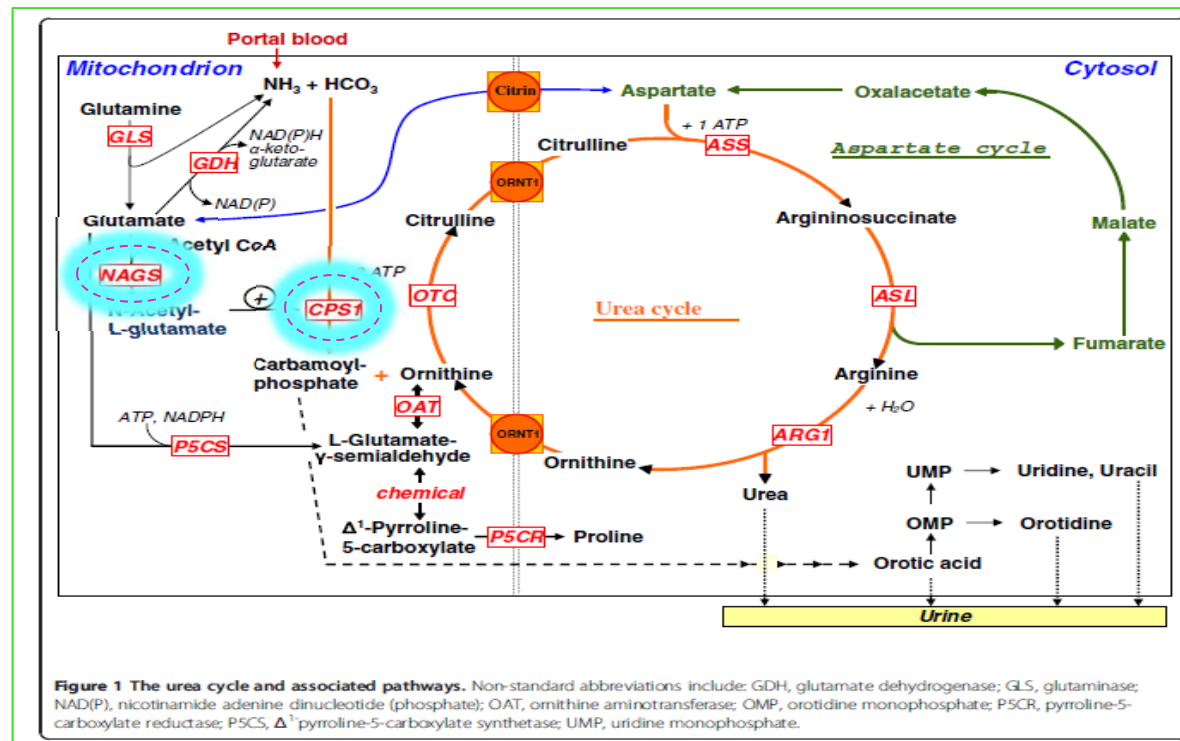
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# N-Acetylglutamate Synthetase Deficiency (NAGSD)



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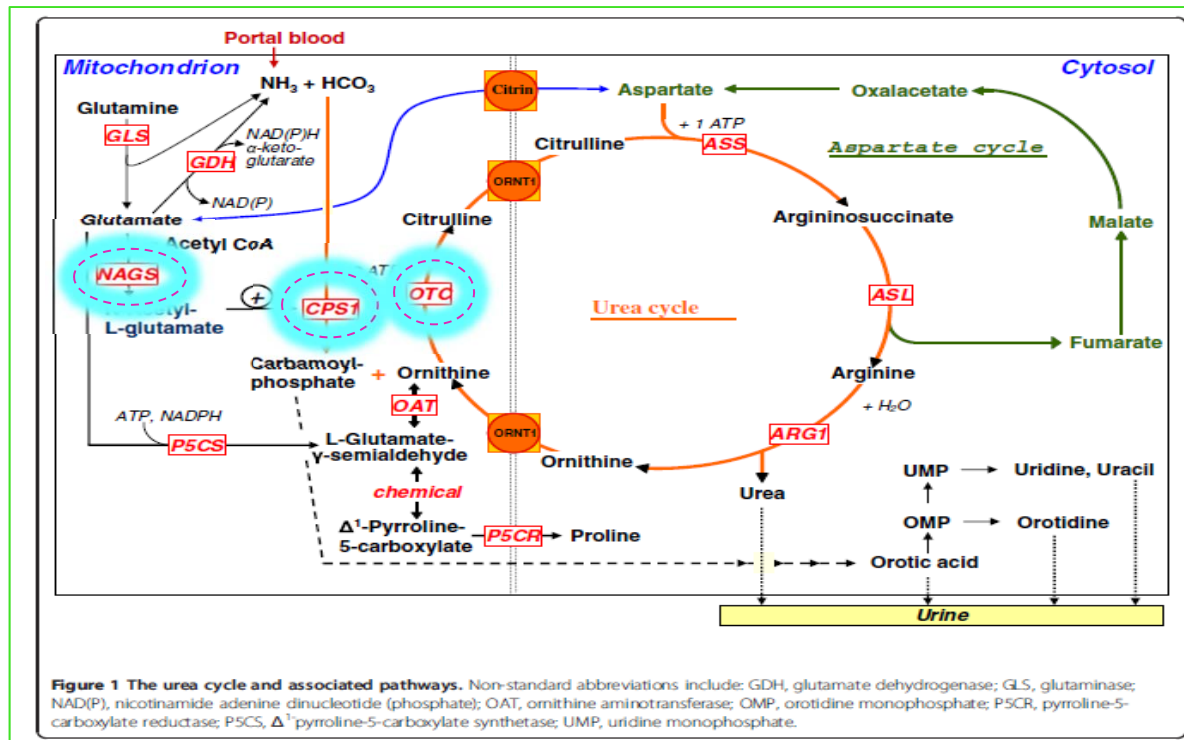
# Carbamyl Phosphate Synthetase 1 Deficiency (CPS1D)



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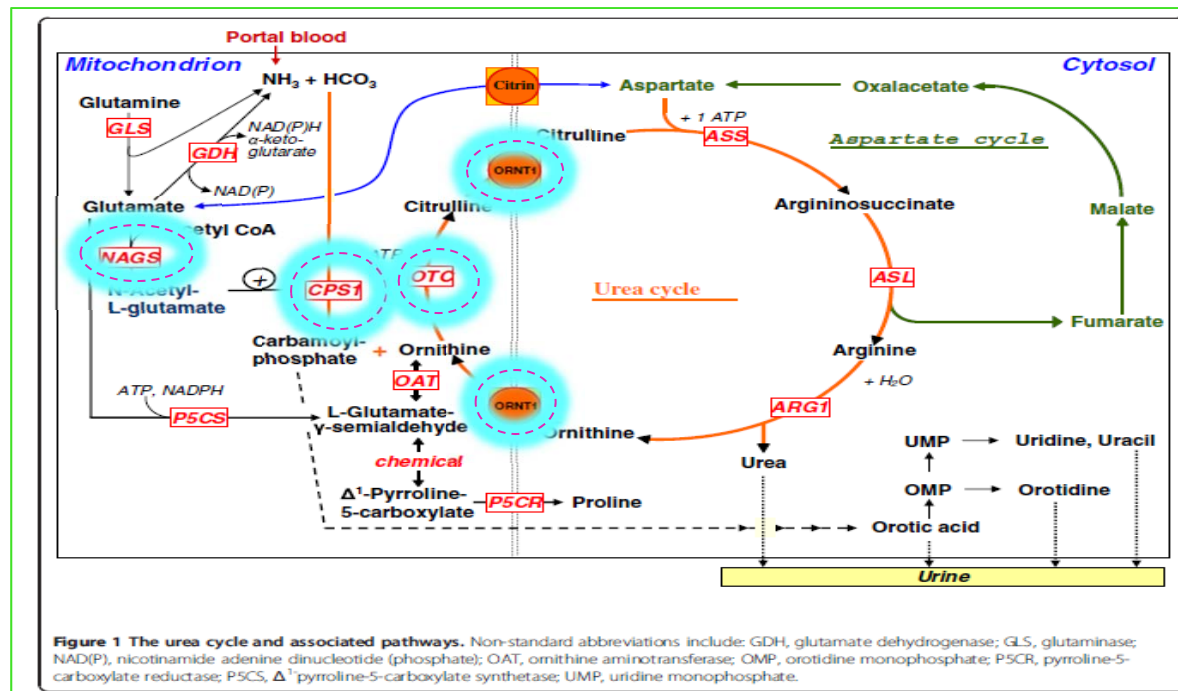


# Ornithine Transcarbamylase Deficiency (OTCD)



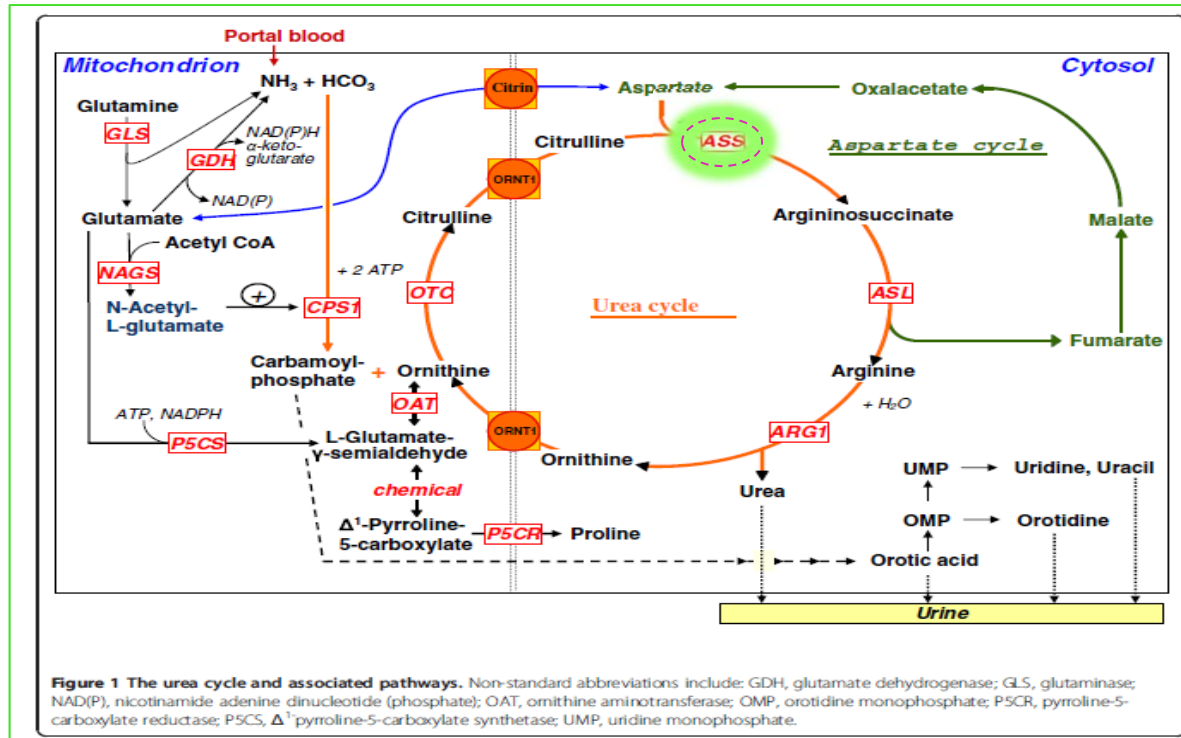
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# Hyperornithinemia-Hyperammonemia-Homocitrullinuria (HHH Syndrome)



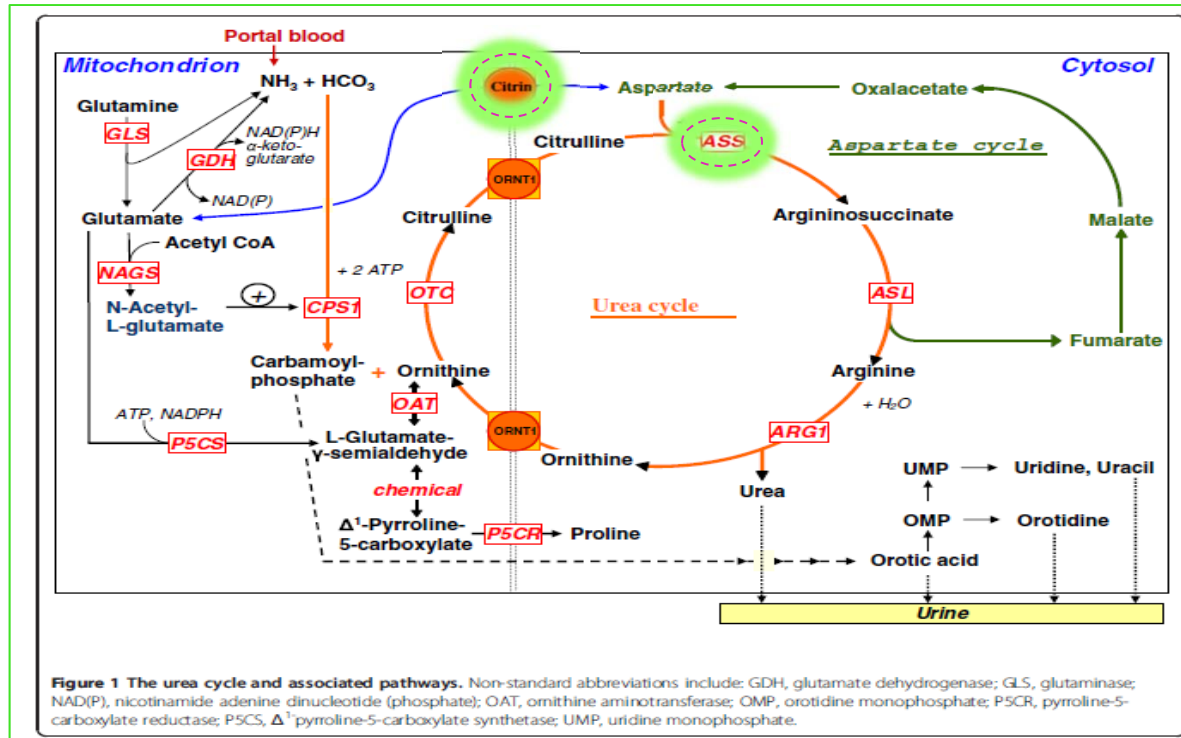
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# UCD Pharmacotherapy



- Primary goal is to reduce and prevent hyperammonemia
  - Nitrogen/ammonia scavengers
    - Sodium benzoate (FDA approved drug - injection solution in combination with sodium phenylacetate for treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle)
    - Sodium phenylacetate (as above)
    - Sodium phenylbutyrate (FDA approved drug - oral tablet for adjunctive therapy in the chronic management of patients with UCDs: CPSD, OTCD, ASSD)
  - Supplementation of amino acids because of impaired synthesis
    - L-arginine, an essential amino acid (FDA approved drug - injectable for non-UCD indication)
    - L-citrulline (not FDA approved drug - chronic, oral use)
  - In NAGSD, N-carbamyl-L-glutamate, or carglumic acid, serves as a NAG analogue (FDA approved drug - oral tablet)



## Use of L-Citrulline in UCDs

- Chronic use of oral L-citrulline supplementation is standard of care in NAGSD, CPS1D, OTCD, and HHH syndrome (Haberle 2012)
  - Precursor to L-arginine in urea cycle
  - Maintain normal protein turnover
  - Promote anabolism and growth in children
- Published dosing recommendations (Singh 2007, Haberle 2012)
- Strong mechanistic rationale based on particular enzyme deficiencies
- No clinical trials were found of L-citrulline in the treatment of UCDs

**Efficacy Conclusion:** Oral L-citrulline is effective in the treatment of certain UCDs

## Recommendation



A balancing of the four evaluation criteria weighs **in favor of** L-citrulline for oral administration being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.







# Pregnenolone

**Pharmacy Compounding Advisory Committee Meeting  
November 20, 2017**

**Wafa Harrouk, PhD**  
Office of Drug Evaluation IV  
Office of New Drugs

# Pregnenolone Review Team



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

**Lesley-Anne Furlong, MD**, Deputy Office Director, ODE IV, OND

**Jean Kim, MD**, Medical Officer, DPP, OND

**Elizabeth Hankla, PharmD**, Consumer Safety Officer, OUDLC, OC

## Nomination

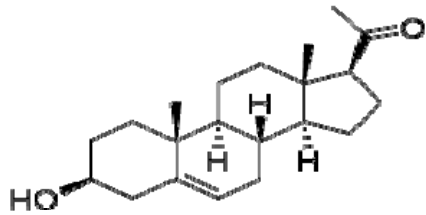


- Pregnenolone has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Proposed uses:
  - For treatment of rheumatoid arthritis
  - For treatment of hypercholesterolemia
  - As adjunctive therapy for schizophrenia
  - As adjunctive therapy for bipolar disorder
- Proposed routes of administration and dose ranges:
  - Oral capsules (5-200 mg), oral suspension (10-200 mg/mL)
  - Topical cream and gel (1-20%)
  - Injection suspension (0.1–5 mg/mL)

# Physical and Chemical Characterization



- Pregnenolone is an endogenous steroid
- Well characterized substance

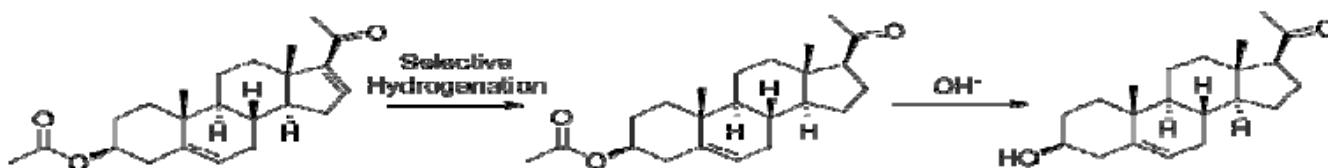


- Insoluble in water
- Likely to be stable under ordinary storage conditions based on chemical structure

## Physical and Chemical Characterization (2)



- Possible synthetic route:

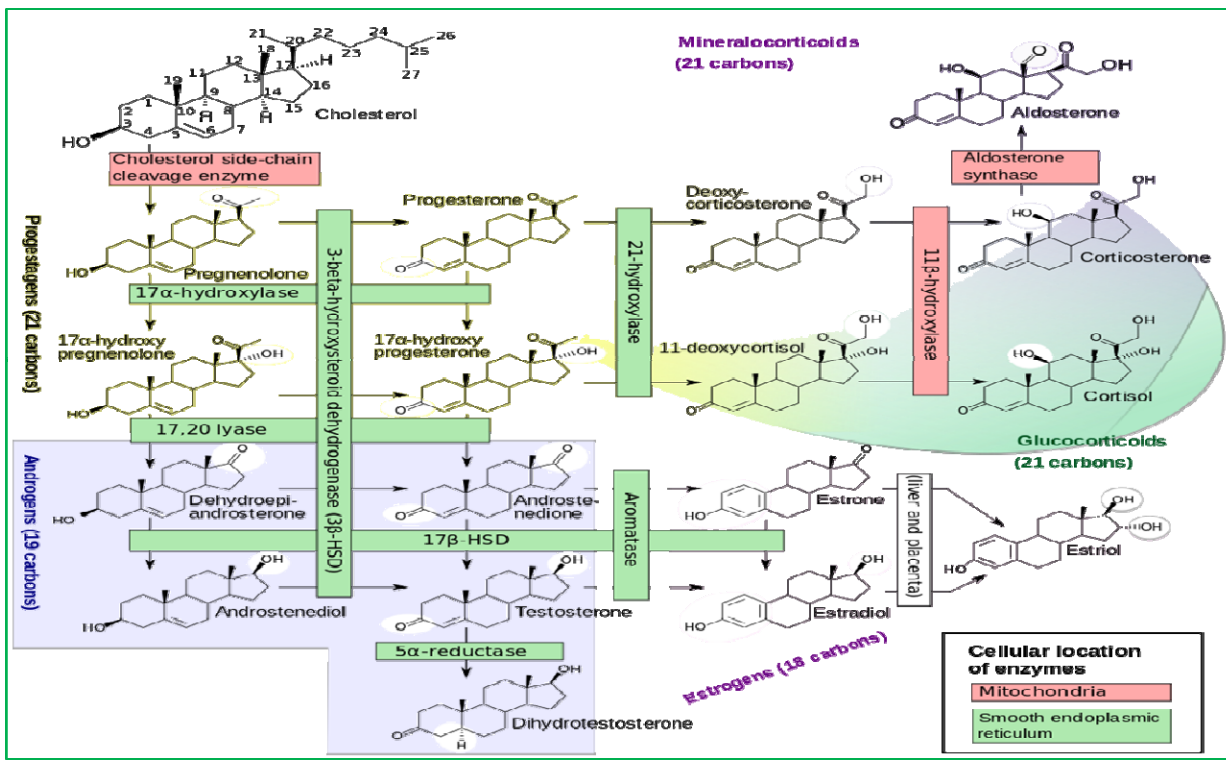


- Impurities include residues from starting materials and are unlikely to be toxic

### Conclusion:

Pregnenolone is a steroid, easily characterized, likely to be stable, and unlikely to have toxic impurities

# General Pharmacology



## Nonclinical Pharmacokinetics/Toxicokinetics



- Metabolic pathways differ among species and among tissues where pregnenolone is expressed
- In rodents, pregnenolone is absorbed from the small intestine with an average time for enterohepatic circulation of approximately 3 hours; it undergoes extensive enterohepatic metabolism
- Pregnenolone can cross the blood brain barrier following intravenous and intranasal administration
- Pregnenolone is metabolized to allopregnanolone, 5- $\beta$  metabolites and sulfated metabolites; it is mostly eliminated in urine
- No toxicokinetic data were found

## Clinical Pharmacokinetics (PK)



- Limited human PK data
- Oral absorption:
  - In a small study (n=3),  $T_{1/2}$  was estimated at 5-25 hours
  - Placebo-controlled study (n=80) measured blood levels of pregnenolone at baseline and end of treatment (doses up to 500 mg/day) showed 4-fold increase in serum pregnenolone in subjects taking pregnenolone
- Transdermal absorption:
  - Found no PK studies supporting transdermal absorption
  - A study (n=10) reported a small decrease in serum levels of pregnenolone from baseline after topical application of a 3% facial cream for four months



# Nonclinical Safety



- Acute dose toxicity show an LD<sub>50</sub> of 5g/kg in mice via the oral route of administration
- Short term repeat dose toxicity in the rat assessing limited toxicology endpoints did not report any toxicities:
  - a- Oral 1g/kg, 3 doses/week for 50 doses: no change in some blood parameters or some visceral weights
  - b- Intraperitoneal injection 0.2 g/kg, 3 doses/week for 50 doses: no change in some blood parameters or some visceral weights
  - c- Oral dosing in food 0.01 and 0.1 g/kg daily for 3 months: no change in weight or food intake
  - d- subcutaneous injection 0.01 g/kg/day for 3 months: no change in weight of some organs
- Repeat dose toxicity assessment was not adequately designed to reveal the toxicity profile of pregnenolone; key parameters such as body weight, clinical observations, gross examination or histopathology assessment were not captured
- No studies were found for chronic toxicity, genotoxicity, developmental/ reproductive toxicity, or carcinogenicity

# Adverse Events: Voluntary Reporting



- FDA Adverse Events Reporting System (FAERS)
  - 7 reports, no serious adverse events (SAEs), adverse events included menopausal symptoms, dizziness, nausea, and excessive hair growth
- CFSAN Adverse Events Reporting System (CAERS)
  - 30 reports, 18 of which reported serious outcomes that included one death and 17 hospitalizations or other serious events. Most commonly reported events (3 or more reports) included increase in heart rate, increase in blood pressure, dizziness, headache, pain, hypersensitivity, dyspnea, anxiety, tremor, and fatigue
- Causality cannot be established due to use of multiple products and/or the use of products containing multiple ingredients

## Adverse Events: Clinical Trials



- Few studies reported systematic collection of adverse events
- Five short-term studies from the 1950's used daily doses from 10 mg to 600 mg (given by intramuscular (IM) injection or IM/oral). Injection site reactions from pain to abscesses were reported as a reason to switch to oral pregnenolone. Other reported adverse reactions included menorrhagia, weight gain, headache, reduced appetite, and depression
- Six short-term studies for adjunctive psychiatric indications (2009-2017) reported no significant safety signals (oral doses from 50 to 500 mg daily)
- No long-term studies were found

## Safety Conclusion



- Insufficient data to support the safety of pregnenolone for treatment of chronic diseases
  - Limited nonclinical data
  - Although there are few adverse events reported for pregnenolone in short term clinical studies, no long term safety data to support the use of pregnenolone for chronic conditions were found
  - Because of its role as a precursor in the production of key steroid hormones, a dose-related increase in adverse events, some serious, may occur with chronic administration of pregnenolone

## Effectiveness: Rheumatoid Arthritis



- Two small (n=10, n=4) uncontrolled case series:
  - Variable response among patients
  - Authors conclude that any of the changes may have been caused by the normal spontaneous variation in rheumatoid arthritis
- Two small (n=21, n=25) controlled clinical trials:
  - No evidence of effectiveness

## Effectiveness: Hypercholesterolemia



- In two uncontrolled retrospective chart reviews:
  - Patients were treated with individually tailored ‘anti-aging’ cocktail of 7 – 9 hormones at varying doses
  - Lack of control group and the use of multiple substances precludes detecting the effect, if any, of any single substance

## Effectiveness: Adjunctive therapy for schizophrenia



- Four reports of randomized, controlled clinical trials
  - Two small exploratory trials with multiple endpoints:
    - One study had 8 subjects treated with pregnenolone that was up-titrated to 500 mg/day
    - The second study had 14 subjects treated with pregnenolone 30 mg/day and 6 subjects treated with 200 mg/day
    - One study used six instruments and the other used ten instruments; no statistical corrections for multiple comparisons were made
    - Both studies reported a trend to improvement in positive subscale of one instrument; however, a typical dose-response relationship was not observed (one study detected trend to improvement at 500 mg/day whereas the other detected trend to improvement at 30 mg/day but not at 200 mg/day)
  - Two larger placebo-controlled trials failed to meet the primary prespecified endpoints
- Data are inadequate to support effectiveness

## Effectiveness: Adjunctive therapy for bipolar disorder



- Two small, randomized, placebo-controlled trials
  - An 8-week exploratory trial: efficacy was measured with six instruments, multiple endpoints and no statistical corrections for multiplicity. More than half of subjects dropped out and almost half had changes in their primary therapy during the trial. Trend in improvement in Hamilton Rating Scale for Depression was reported.
  - A 12-week study showed a trend in improvement of Hamilton Rating Scale for Depression that was not statistically significant
- Data are inadequate to support effectiveness



## Effectiveness: Conclusion



- Data do not support concept that pregnenolone is effective in treating rheumatoid arthritis or hypercholesterolemia
- Data are inadequate to support that pregnenolone is an effective adjunctive therapy for schizophrenia or bipolar disorder
- All four conditions are chronic conditions that can be serious, depending on the severity and associated comorbidities
- There are numerous FDA-approved drug therapies for each of the nominated uses

## Historical Use in Compounding



- Used in pharmacy compounding in the United States in a wide range of conditions since at least 2003
- Use reported in Australia in compounded hormone replacement therapy
- Not listed in the British, European, or Japanese Pharmacopoeias
- Currently available as a dietary ingredient in dietary supplement products

## Recommendation



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





# 7- Keto Dehydroepiandrosterone (7-keto DHEA)

**Pharmacy Compounding Advisory Committee Meeting  
November 20, 2017**

**Susan Johnson, PharmD, PhD**  
Associate Director  
Office of Drug Evaluation IV  
Office of New Drugs

## 7-keto DHEA Review Team



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

**Lesley-Anne Furlong, MD**, Deputy Director, ODE IV, OND

**Elizabeth Hankla, PharmD**, Consumer Safety Officer, OUDLC, OC

# Nomination

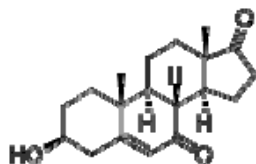


- 7-keto DHEA has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Proposed uses:
  - Weight loss/treatment of obesity
  - Treatment of Raynaud’s phenomena
- Proposed routes of administration:
  - Oral
  - Sublingual
  - Topical

# Physical and Chemical Characterization



- Small, endogenous steroid molecule



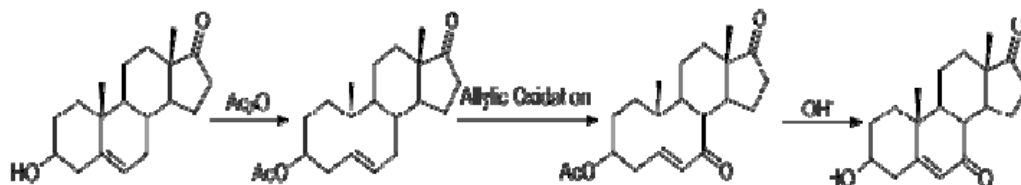
- Well characterized structure
- Practically insoluble in water
- No stability data available
  - Structure suggests it is likely to be stable under ordinary storage conditions in oral or topical formulation



## Physical and Chemical Characterization (2)



- Possible synthetic route:
  - Synthesized via the allylic oxidation of DHEA
  - Impurities may include heavy metals used as catalysts



### Conclusion:

- 7-keto DHEA is well characterized
- Likely to be stable in oral, sublingual and topical formulations under normal storage conditions

# General Pharmacology



- Endogenously produced in multiple organs from the metabolism of DHEA
  - DHEA is a substrate for the production of testosterone and estrogen
  - DHEA is converted to 7 $\alpha$ -hydroxy DHEA or 7 $\beta$ -hydroxy DHEA, which are in turn converted to 7-keto DHEA
  - There is variation in the literature about whether 7-keto DHEA can be converted, through the hydroxy steroids, to DHEA
- Results of in vitro studies suggest:
  - Indirect induction of estrogen-mediated gene expression (Miller 2013)
  - Lack of androgenic activity (Mo 2006)
  - May help regulate conversion of inactive to active cortisol as a “native anti-glucocorticoid” (Muller 2006)
- World Anti-Doping Agency classifies 7-keto DHEA as an “S1 Anabolic Agent”
  - No data identified to clarify the basis of the classification

# Pharmacokinetics



- Study of endogenous levels of 7-keto DHEA in 8 women of reproductive age (Starka 2015)
  - Mean plasma levels ranged between 0.6 nmol/L (181.4 ng/L) and 0.4 nmol/L (120.9 ng/L) at 12 collection time points between 6 AM and 9:30 PM
- Topical administration of gel (25 mg 7-keto DHEA daily) for 5 days in 10 healthy male subjects (Sulcova 2001)
  - No measure of 7-keto DHEA reported
  - Significant decline in plasma testosterone and estradiol
  - Significant increase in plasma lutenizing hormone, high density lipoprotein, apolipoprotein A-I, apolipoprotein B and lipoprotein (a)
- Topical administration of gel (25 mg 7-keto DHEA daily) for 8 days in 21 healthy male subjects with assessment out to 100 days following dosing (Sulcova 2005)
  - Significant decrease in 7 $\alpha$ -hydroxy DHEA, testosterone, estradiol and sex hormone binding globulin out to 91 days after dosing
  - Significant increase in 7 $\beta$ -hydroxy DHEA for 28 days and epitestosterone for 100 days after dosing



## Nonclinical Safety

- No data were found for 7-keto DHEA:
  - Acute toxicity
  - Genotoxicity
  - Developmental and reproductive toxicity
  - Carcinogenicity
- Repeat dose toxicity for 7-keto DHEA in 16 Rhesus monkeys (Henwood 1999)
  - Treatments: 2 animals dosed for 1 week at 7 mg/kg/day  
2 animals dosed for 1 week at 35 mg/kg/day  
3 animals dosed for 2 weeks at 70 mg/kg/day  
3 animals dosed for 26 days at 140 mg/kg/day  
3 animals doses with placebo and 3 animals doses with 25 mcg thyroxin
  - No adverse events; no change in clinical chemistries or liver biopsy: NOAEL 140 mg/kg
- Nonclinical safety studies with 7-oxo DHEA acetate
  - No-Observable Adverse Effect Level (NOAEL) of 500 mg/kg in 5 Rhesus monkeys dosed up to 5 days; vomiting at 1000 mg/kg (Henwood 1999)
  - Negative AMES test

# Clinical Safety



- Adverse Events
  - FDA Adverse Event Reporting System (FAERS)
    - 1 case: Male patient reported a 5 fold increase in testosterone levels after taking 7-keto DHEA acetate for 60 days. No additional information.
  - CFSAN Adverse Event Reporting System (CAERS)
    - 14 reports: Confounded by use of multiple supplements preventing causality assessment
  - No clinical trials to assess safety or safety data from other trials
  - No published case reports providing safety data

## **Safety Conclusion:**

- Very limited safety data available
- Cannot rule out safety concerns, especially for long term use

# Efficacy



- Raynaud's phenomena
  - Vasospasm of the arteries and arterioles of the extremities, particularly fingers and toes
  - No clinical trials found
  - 1 case report of improvement in a single patient during use; recurrence on discontinuation
- Weight Loss / Treatment of Obesity
  - No interventional clinical trials

## **Efficacy Conclusion:**

Insufficient evidence to establish that 7-keto DHEA is effective in weight loss/treatment of obesity or the treatment of Raynaud's phenomena

## Historical Use in Compounding



- Based on published literature, 7-keto DHEA has been used in pharmacy compounding for at least 7 years
- Extent of use cannot be determined
- 7-keto DHEA is not listed in the British, European, or Japanese Pharmacopeias
- Currently available as a dietary ingredient in dietary supplement products, as is 7-keto DHEA acetate

## Recommendation



A balancing of the four evaluation criteria weighs **against** 7-keto DHEA being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.







# Astragalus Extract 10:1

**Pharmacy Compounding Advisory Committee Meeting  
November 20, 2017**

**Michael Brave, MD, Clinical Reviewer**  
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Office of Hematology and Oncology Products (OHOP)

## Review Team



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## Nomination



- Astragalus 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)
- Use: For diabetes mellitus, allergic rhinitis, wound healing, asthma, and herpes simplex keratitis
- Route of administration: Oral

# Physical and Chemical Characterization



- Complex botanical raw material
  - Traditional Chinese medicine (TCM) plant species:
    - *Astragalus membranaceus* (Fisch.) Bunge
    - *Astragalus membranaceus* (Fisch.) Bunge var. *Mongholicus* (Bunge)
  - Dried root (radix) is used in TCM
- Details of the manufacturing/extraction process of Astragalus extract 10:1 are not provided in the nomination
  - Extraction solvent(s)
  - Ratio of solvent to raw materials
  - Extraction conditions, e.g., temperature



# Chemical Components



- A complex mixture of different classes of compounds have been identified in astragalus root
  - Polysaccharides are commonly the major components in the aqueous astragalus extract
  - Known polysaccharides: such as astragalan I, II, III, etc.
  - Triterpene glycosides: such as astragalosides I - VII
  - Flavonoids: more than twenty flavones and flavonoid glycosides
  - Other constituents: trace elements, amino acids, etc.
- Key active ingredients are unknown

# Astragalus Dietary Supplements



## Characterization - Conclusion



- Astragalus root and extracts used in TCM contain a complex mixture of compounds.
- Insufficient information was provided to fully characterize the nominated substance.





# Nonclinical Toxicology

# Nonclinical Pharmacokinetics



## Astragaloside IV

- Low GI absorption and bioavailability in the rat and dog
- Rapidly absorbed and widely distributed after IV administration
- Highly bound to plasma protein (approximately 90%)
- Recovery in urine and feces is approximately 50%
- Mainly eliminated as metabolites

## Glucuronides

- Plasma concentrations much higher than Astragalus parent compounds after oral consumption
- Mean half-life was between 1 and 5 h
- Metabolites were eliminated faster than the parent compound



## Repeat-Dose Toxicity

- 90-day study in rats<sup>1</sup>
  - Radix astragali extract: 5.7, 15.08, or 39.9 g/kg/day IP
  - No toxicity observed
- 90-day study in dogs<sup>1</sup>
  - Radix astragali extract: 2.85, 7.54, or 19.95 g/kg/day IP
  - No toxicity observed
- 91-day study in rats<sup>2</sup>
  - Cycloastragenol: 40, 80, or 150 mg/kg/day orally
  - No toxicity observed

<sup>1</sup> Yu S, et al. J Ethnopharmacol 2007;110:352

<sup>2</sup>Szabo NJ, et al. Food Chem Toxicol 2014;64:322

# Genotoxicity, Carcinogenicity, and Reproductive Toxicity



- **Genotoxicity**
  - Mixed results of chromosomal aberration assays for various astragalus extracts
  - No definitive conclusion can be made
- **Carcinogenicity**
  - No studies identified
- **Reproductive Toxicity**
  - Astragaloside-IV administered intravenously to rats and rabbits. Led to an increase in fetal death in both species; in rats only, decreased body weight in dams and developmental delay in offspring

## Toxicology Summary



- There are no data for the nominated 10:1 extract
- No toxicity observed in repeat dose studies of other astragalus extracts in dogs and rats
- Genotoxic potential unknown
- No carcinogenicity data identified
- Fetal deaths observed in rats and rabbits dosed with astragaloside-IV



## Clinical Information

## Adverse Events: Voluntary Reporting



Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS) search (June 27, 2017):

- 547 reports (7 describe astragalus as sole ingested product)
- 4 deaths reported, none with astragalus as the sole ingested product
- Predominant organ systems affected: GI (54% of cases), cardiac (9%), general (9%), allergy/hypersensitivity (7%), hepatobiliary (4%), other (17%)

## Safety Conclusion



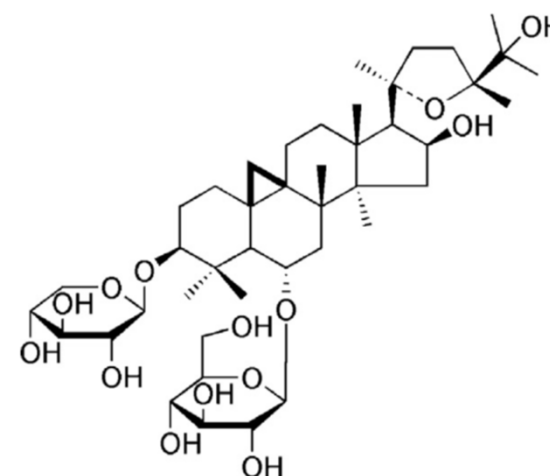
- Published reports of clinical effects do not analyze or discuss adverse reactions
- Center for Food Safety and Nutrition Center's Adverse Event Reporting System contained 547 varied case reports as of June 27, 2017



## Clinical Pharmacokinetics



- Astragaloside-IV is reportedly pharmacologically active
- Phase I trial in 40 healthy Chinese volunteers\*
  - Single-dose oral PK linear over 200 ml to 500 ml dose range.
  - Only 4% of astragaloside IV excreted unchanged in urine.
  - Accumulation not observed in 16 volunteers given 500 ml doses daily for 7 days.



**Astragaloside-IV**

\* Xu M, et al. Phytomedicine 2013;20:1105

## Clinical Trial Considerations



Generally, individual studies and meta-analyses:

- Did not provide details about the astragalus preparation used. Therefore, it is unclear whether the results are applicable to the nominated substance.
- Were apparently conducted using a variety of methodologies. These were not well described in the publications.
- Suggest minor treatment effects on a subset of assessed endpoints. We cannot conclusively interpret these findings as substantive clinical benefit.

## Effectiveness in Diabetes Mellitus



Tian performed a meta-analysis of 13 clinical trials (1054 total subjects) comparing astragalus (by oral or intravenous administration) to usual care in patients with type 2 diabetes mellitus. All 13 trials were conducted in China. The analysis concluded that astragalus by either route of administration reduced fasting plasma glucose, postprandial plasma glucose, and insulin sensitivity. Only the aqueous decoction reduced HbA1c levels.

Tian H, et al. J Ethnopharmacol 2016;191:206

## Effectiveness in Diabetes Mellitus



Li performed a meta-analysis of 21 randomized controlled trials and 4 uncontrolled trials of astragalus which enrolled a total of 1804 patients (945 in treatment group and 859 in control group) with diabetic nephropathy. All trials were conducted in China. The analysis concluded that astragalus may improve proteinuria and serum creatinine in these patients.

Li M, et al. J Ethnopharmacol 2011;133:412

## Effectiveness in Diabetes Mellitus



Kim (2014) reported a case of a 62 year old man with diabetic neuropathy who attained short-term improvement in proteinuria and glomerular filtration rate following administration of *Astragalus membranaceus* extract.

Kim J, et al. Endocrinol Diab Metab Case Rep 2014:140063

## Effectiveness in Diabetes Mellitus



Chao randomized 43 patients with newly diagnosed type 2 diabetes mellitus to traditional Chinese medicine (3 mg of a mixture of 50 mg of *Coptis chinensis*, 30 mg of *Astragalus membranaceus* [sic], and 120 mg of *Lonicera japonica*) vs. placebo three times daily before meals. At 3 months, patients in the investigational arm had less insulin resistance compared to baseline.

Chao M, et al. *Endocrine* 2009;36:268

## Effectiveness in Diabetes Mellitus



Lien performed a retrospective analysis comparing 416 Taiwanese patients with type 1 diabetes mellitus whose treatment included traditional Chinese herbs (some of which contained astragalus) to 1608 matched case-control patients with type 1 diabetes mellitus who did not use traditional Chinese herbs. The analysis concluded that Chinese herbal therapy may reduce the incidence of diabetic ketoacidosis.

Lien AS, et al. J Ethnopharmacol 2016;191:324.

## Effectiveness in Diabetes Mellitus



Pang (2016) performed a meta analysis of 16 randomized controlled trials (1173 patients) of *Huangqi Guizhi Wuwu* a traditional Chinese herbal decoction (composed of *Radix Astragali seu Hedysari*, *Ramulus Cinnamom*, *Radix Paeoniae Alba*, *Rhizoma Zingiberis Recens* and *Fructus Jujubae*) for the treatment of patients with diabetic peripheral neuropathy. All trials were conducted in China. The analysis concluded that *Huangqi Guizhi Wuwu* improved diabetic neurologic symptoms and nerve conduction velocities.

Pang, et al. Neural Regen Res 2016;11:1347



## Effectiveness in Allergic Rhinitis



Matkovic (2010) randomized 48 adults with seasonal allergic rhinitis to 6 weeks of treatment with an herbal mineral complex containing *Astragalus membranaceus* vs. placebo. The authors found patients in the active treatment group to have a trend toward symptomatic improvement, but no significant change in serum IgE or IgG or nasal eosinophils.

Matkovic Z, et al. *Phytother Res* 2010;24:175

## Effectiveness in Wound Healing



Ko randomized 16 patients with type 1 or type 2 diabetes mellitus and mild diabetic foot ulceration to a mixture of Astragali Radix and Rehmanniae Radix vs. placebo twice daily. At 6 months, patients in the investigational arm showed a trend toward improved wound healing.

Ko CH, et al. J Diabetes 2014;6:323

## Effectiveness in Asthma



- Wong randomized 85 children with asthma who were using inhaled corticosteroids to a daily oral combination of five herbs including an astragalus vs. placebo for 6 months. The trial failed to show a reduction in steroid dosage or improvement in lung function or biochemical markers of disease.
- A meta-analysis by Bang of 18 randomized trials of pharmacopuncture, including four studies using Radix Astragali, suggested improved lung function compared to conventional therapy.

Wong EL, et al. J Altern Compl Med 2009;15:1091  
Bang M, et al. Eur J Integ Med 2017;11:6-17

## Effectiveness in Herpes Simplex Keratitis



We found no published reports of astragalus affecting clinically meaningful endpoints in patients with herpes simplex keratitis.

## Effectiveness Conclusion



- Traditional Chinese medical literature contains reports of astragalus for diabetes mellitus, allergic rhinitis, wound healing, and asthma
- Most studies involved multiple herbs, none of which appear to have been the 10:1 nominated substance
- Most reports lacked statistical analysis plans for clinically meaningful efficacy endpoints
- No long-term data are available

## Historical Use in Compounding



- Astragalus has been used in traditional Chinese medicine for thousands of years
- Listed in multiple compendia
  - Defined in the Pharmacopoeia of the People's Republic of China (2015 Edition)
  - European Pharmacopoeia (9th Edition, 2017)
  - British Pharmacopoeia (2017)
  - Japanese Pharmacopoeia (16th Edition)
- Information is insufficient to determine if nominated astragalus 10:1 has been used in compounding, as the nominated substance has not been characterized

## Summary



- Nominated substance is not adequately characterized.
- Safety concerns in nonclinical reproductive toxicity studies and CAERS data.
- Nonclinical models suggest some compounds isolated from astragalus species have therapeutic potential for patients with diabetes mellitus, wound healing, asthma and herpes simplex keratitis.
- Nonclinical and clinical findings have not yet translated to effects on endpoints associated with clinical benefit in any patient population.
- Astragalus preparations are used in TCM, but information is insufficient to determine if the nominated substance has been used in compounding.

## Recommendation



A balancing of the four evaluation criteria weighs **against** Astragalus extract 10:1 being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.







# Epigallocatechin Gallate (EGCG)

**Pharmacy Compounding Advisory Committee Meeting  
November 20, 2017**

**Susan Johnson, PharmD, PhD**  
Associate Director  
Office of Drug Evaluation IV  
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# Nomination

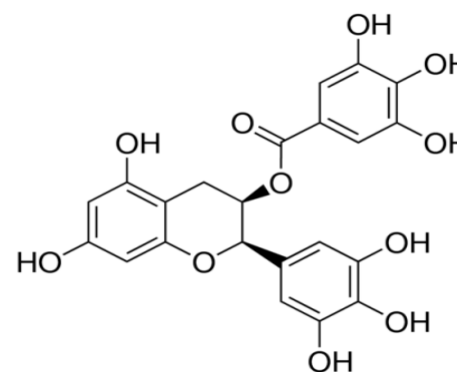


- EGCG has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug and Cosmetic Act (FD&C Act)
- Proposed uses:
  - Obesity
  - Type 1 and type 2 diabetes
  - Cardiac hypertrophy
  - Corneal neovascularization
  - Non-alcoholic fatty liver disease (NAFLD)
  - Parkinson’s disease
  - Wound healing
- Proposed routes of administration:
  - Oral (200 mg capsules)
  - Ophthalmic (0.25 - 1% solution)
  - Topical (1% gel)

# Physical and Chemical Characterization



- Polyphenol, catechin compound
- EGCG has a well characterized structure
  - Nominated substance is  $\geq 94\%$  EGCG
  - Other components are not identified in nomination
- Soluble in water
- Unlikely to be stable under ordinary storage conditions
  - Solid stable for one week; 13% degraded at the end of one month
  - Solution subject to oxidation and degradation; 20% degraded after 6 days



## Physical and Chemical Characterization (2)



- Possible synthetic routes
  - Usually extracted from green tea leaves when used for commercial products
  - Chemical synthesis is complicated, expensive and has a low yield

### **Conclusion:**

- EGCG is well characterized; nominated substance is at least 94% EGCG
- Unlikely to be stable in oral, ophthalmic and topical formulations under normal storage conditions

# Background



- EGCG is abundant in green tea (GT) leaves
  - 20 - 80% of GT extract
  - Also found in black, oolong tea; various edible plants & nuts
  - USDA survey of 24 green teas sold in the U.S. used boiling water extraction; found EGCG content ranged from 2.2 to 53.6 mg per gm of dry tea leaves
- Substantial research and information on GT and GT extract
  - Validity of extrapolation of GT data to EGCG is unknown; however, GT data may suggest hypotheses regarding EGCG safety or efficacy that would require further evaluation
- Component of FDA approved topical botanical product
  - Veregen® for the treatment of genital and perianal warts
  - Active ingredient is sin catechins, a proprietary extract of green tea comprised of 55% EGCG
  - Does not establish EGCG as an approved drug
  - Proposed uses are not the same as approved indication for FDA approved product

# General Pharmacology of EGCG



- **Weight loss/treatment of obesity**
  - Potential to increase fat oxidation in obese men (Boschmann and Thielecke 2007)
- **Diabetes**
  - In vitro decrease in glucose production in rat hepatoma cells similar to insulin (Waltner-Law 2002)
  - Reduced mouse islet cell destruction by streptozocin in vivo (Song et al. 2003)
- **Cardiac hypertrophy**
  - In vivo rat models show suppression of load-induced heart weight (Hao et al. 2007) and cardiomyocyte apoptosis (Sheng et al. 2013)
- **Corneal neovascularization**
  - Multiple in vitro and in vivo studies suggest potential anti-angiogenic mechanism of action (Chang et al. 2017)



## General Pharmacology of EGCG (2)



- Parkinson's disease
  - Multiple in vitro and in vivo animal studies suggest potential neuroprotective mechanism of action via molecular targets such as AKT, protein kinase C and mitogen-activated protein kinase
- NAFLD
  - Multiple in vivo animal studies suggest mechanisms of action to increase lipid oxidation, improve insulin resistance and decrease NAFLD-related fibrosis
- Wound healing
  - Wound healing in mouse model of Type 2 diabetes improved (reepithelialization, formation of blood vessels and induction of myofibroblasts) with EGCG; high dose toxicity



# Pharmacokinetics

- Nonclinical pharmacokinetics
  - Oral bioavailability in rats 0.1 - 5%; modestly higher in dogs and mice
  - Increased bioavailability in fasted state
  - Once absorbed, EGCG distributes primarily to intestines, kidney, liver and lungs
  - Biliary excretion
- Clinical pharmacokinetics
  - In humans, EGCG has low oral bioavailability (0.2 - 2%)
  - Multiple presystemic processes in small intestine
    - High solubility results in poor membrane permeability
    - Undergoes extensive intestinal metabolism (methylation, glucuronidation, sulfation)
    - Efflux transporter-mediated intestinal excretion
  - First pass metabolism
  - Metabolized by gut microflora in the large intestine
  - 3-5 fold increase in plasma EGCG when fasted
  - Methods being investigated to improve bioavailability (e.g., prodrugs, analogs, carriers)

# Nonclinical Safety - EGCG Studies



- Acute toxicity
  - Hepatotoxicity in fasted mice seen with intragastric doses of 100% EGCG at 500 mg/kg and above; deaths at 1500 mg/kg (Lambert 2010)
- We found no studies of these types conducted with doses of 100% EGCG
  - Repeat dose toxicity
  - Genotoxicity
  - Developmental and reproductive toxicity
  - Carcinogenicity

# Nonclinical Safety – National Toxicology Program (NTP)



- NTP (2016) report on testing GT extract preparation containing 48.4% (w/w) EGCG
- Repeat dose toxicity
  - 2 years daily exposure of GT preparation at doses of up to 1000 mg/kg in rats and 300 mg/kg in mice
  - NOAEL 100 mg/kg in both rats and mice
  - In rats, high dose associated with increased incidence of mortality and hepatic & stomach mucosal necrosis; lesions of multiple organs
  - In mice, no deaths were seen; liver inflammation and hematopoietic cell proliferation at  $\geq$  300 mg/kg
- Genotoxicity
  - Ames assay was positive in 2 bacterial strains in the presence of metabolic induction (using rat liver in the presence of S9). No positive signal was seen in the absence of metabolic induction in these strains, in other strains or using other in vivo assays.
  - No mutagenicity was seen in vivo when using peripheral blood erythrocytes collected from mice treated for 3 months (up to 1000 mg/kg EGCG)

## Nonclinical Safety - NTP (2)



- Developmental and reproductive toxicity
  - After 3 months of dosing in rats, the highest dose used was associated with minor changes in reproductive organ weights in males and longer estrous cycles in females compared to placebo
- Carcinogenicity
  - The only tumors were noted in 2 female mice in 300 mg/kg GT preparation group developed squamous cell neoplasms of the tongue
  - Questionable relevance due to low incidence and lack of dose relationship

# Voluntary Reporting of Adverse Events



- FDA Adverse Event Reporting System (FAERS)
  - 4 cases, excluding Veregen<sup>®</sup> or Hydroxycut (dietary supplement) cases
    - EGCG - 1 case of possible drug interaction to increase cyclosporine levels
    - GT extract - 3 cases of hepatotoxicity with temporal relationship, positive dechallenge and one positive rechallenge
- CFSAN Adverse Event Reporting System (CAERS)
  - 200 cases of EGCG or GT products
    - 72 cases with Hydroxycut
    - 128 reports confounded by use of other drugs or dietary supplements
      - 5 reports of liver injury
      - 6 reports of liver failure; one required transplant
      - 2 cases of burning, swelling, etc in association with topical use of moisturizer product containing GT

# EGCG Adverse Events from Published Literature



- Weight loss/treatment of obesity
  - 3 month study of 83 obese postmenopausal women taking 300 mg EGCG daily or placebo (Mielgo-Ayuso et al. 2014)
    - EGCG from marketed green tea extract preparation claiming to have 97% EGCG content
    - No changes in liver transaminases and no discontinuations due to adverse events
  - 12 week study in 38 obese or overweight pre-menopausal women taking 150 mg EGCG or placebo (Hill et al. 2007)
    - EGCG from marketed green tea extract preparation claiming to be at least 94% EGCG
    - Measures of liver function, hematology and serum electrolytes remained normal
- No safety data on EGCG from studies of diabetes, cardiac hypertrophy, corneal neovascularization, Parkinson's disease, NAFLD and wound healing
- Case reports and safety data for GT products
  - Hepatotoxicity, liver transplantation and death due to liver failure

## Safety Conclusion



- Limited safety data available from studies of EGCG
  - Relevance of data derived from exposure to GT preparations is unclear
- Hepatotoxicity was seen in nonclinical and clinical data in association with GT preparations containing EGCG
  - Potential causal relationship with EGCG can not be fully assessed



# EGCG Efficacy: Weight Loss/Treatment of Obesity



- 3 month study of 83 obese postmenopausal women taking 300 mg EGCG or placebo daily (Mielgo-Ayuso et al. 2014)
  - EGCG from marketed green tea extract preparation claiming to have 97% EGCG content
  - No difference between groups overall in waist circumference, total body fat, abdominal fat, intra-abdominal adipose tissue, blood pressure, lipids, insulin or glucose
  - In patients with impaired glucose tolerance, significant decrease in resting heart rate and plasma glucose
- 12 week study in 38 obese or overweight pre-menopausal women taking 150 mg EGCG or placebo (Hill et al. 2007)
  - EGCG from marketed green tea extract preparation claiming to be at least 94% EGCG
  - No significant difference between groups in the change in body weight, fat mass, energy and fat metabolism, lipids or insulin resistance

## EGCG Efficacy: Type 1 and 2 Diabetes



- 404 pregnant women in their third trimester taking 500 mg EGCG or placebo daily until full term (Zhang et al. 2017)
  - EGCG apparently from bulk chemical containing at least 95% EGCG
  - At full term, EGCG group had significantly lower fasting plasma glucose, insulin levels and insulin resistance
  - Of the 57 patients who had to begin insulin treatment before full term, 16 (28%) were from the EGCG group
- 8 week study of 88 overweight or obese males taking 400 mg EGCG or placebo (Brown, et al. 2009)
  - EGCG from marketed green tea extract preparation claiming to have more than 97% EGCG content
  - No difference between groups on insulin sensitivity, insulin secretion, glucose tolerance, or metabolic parameters except reduction in diastolic blood pressure

## EGCG Efficacy: Other Proposed Uses



- Parkinson's disease
  - Single study of “green tea polyphenols” conducted with 410 newly diagnosed patients in China 2006 - 2009 (ClinicalTrials.gov Identifier NCT00461942)
  - No publication or data were found, but on the Michael J. Fox Foundation for Parkinson's Research website there is a summary of a study that could be the one referenced above
  - The investigators concluded that “green tea polyphenols appear to provide, at least, a mild symptomatic benefit in early untreated Parkinson's disease”
- No clinical efficacy data were identified for the use of EGCG in:
  - Cardiac hypertrophy
  - Corneal neovascularization
  - NAFLD
  - Wound healing

### **Efficacy Conclusion:**

There is insufficient evidence to establish that EGCG is effective for any of the proposed uses

## Historical Use in Compounding



- EGCG was first isolated from tea in 1944 but there is insufficient information to determine:
  - How long it has been used in pharmacy compounding
  - The extent of its use in compounded drug products
- EGCG is not listed in the British, European or Japanese Pharmacopeias
- Currently available as a dietary ingredient in dietary supplement products, as are green tea and green tea extracts

## Recommendation



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





# Resveratrol

**Pharmacy Compounding Advisory Committee Meeting  
November 20, 2017**

**Charles Ganley, MD**

Office Director, Office of Drug Evaluation IV  
Office of New Drugs

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**Elizabeth Hankla, PharmD**, Consumer Safety Officer, OUDLC, OC

**Charles Ganley, MD**, Office Director, ODE IV, OND



# Nomination

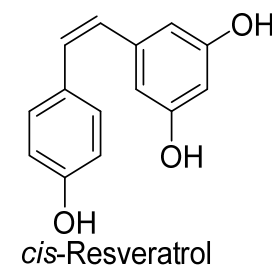
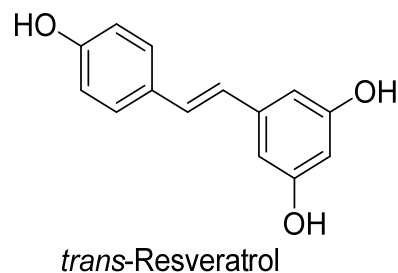


- Resveratrol (trans-3,4',5-trihydroxystilbene) has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Proposed uses for the treatment of:
  - Impaired glucose tolerance in older adults
  - Pain (unnominated but reviewed by FDA)
- Reviewed routes of administration: oral, topical
- No specific dosage forms or strengths were proposed

# Physical and Chemical Characterization



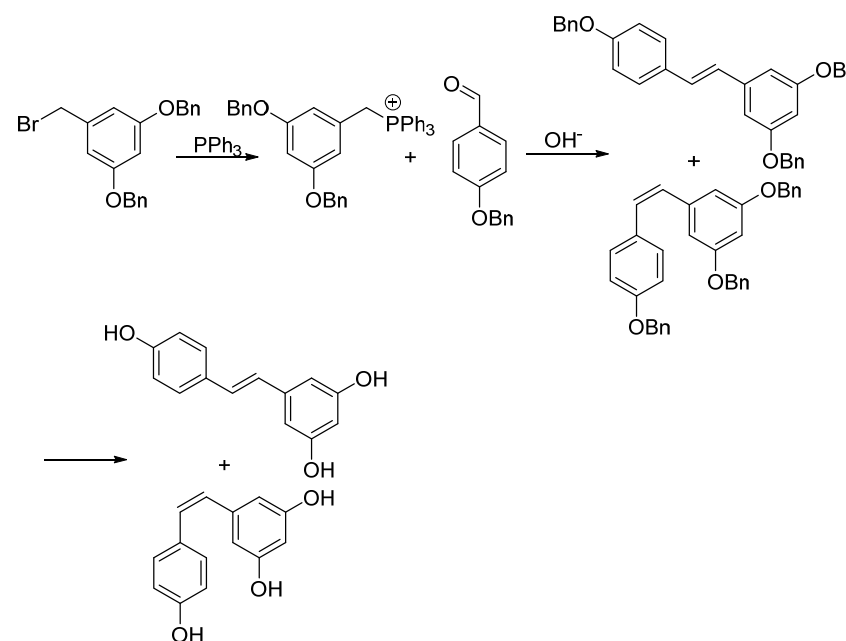
- Resveratrol is a naturally occurring polyphenolic phytoalexin
- It is a stilbenoid with two well characterized structural isomers, cis and trans; the trans is the more abundant and bioactive isomer
- Trans-resveratrol is slightly soluble in water
- Trans-resveratrol is more stable when kept away from light
  - Exposure to light causes acceleration of isomerization between the cis and trans isomers, the cis being the less stable isomer; light induced degradation of cis-resveratrol leads to genotoxic impurity



## Physical and Chemical Characterization (2)



- Some plants produce small quantities of resveratrol in response to pathogens
- Large scale quantities can be chemically synthesized
- Synthesized resveratrol is a mixture of trans and cis isomers (7:3 ratio)
- The two isomers can be isolated with chromatography



## General Pharmacology



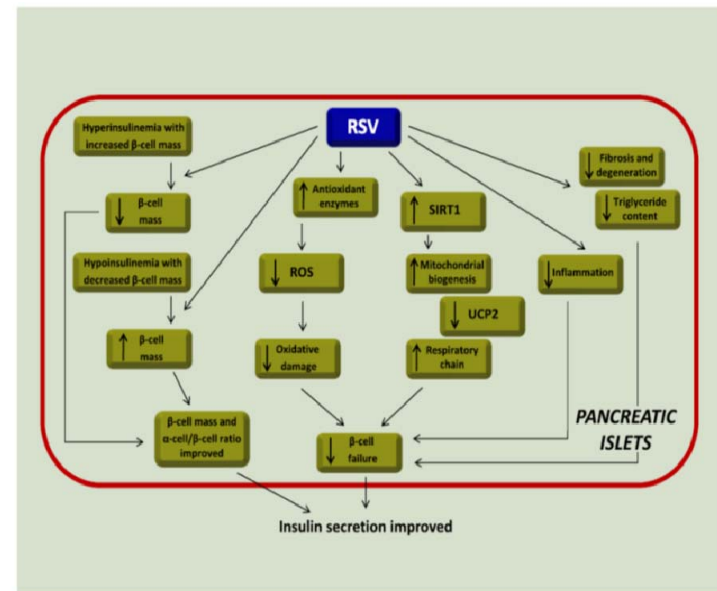
- Resveratrol's anti-oxidative properties (dose-dependent; 1 to 100  $\mu\text{mol/L}$ ; Wallerath et al 2002) were shown to be mediated by upregulation of endothelial nitric oxide and scavenging free radicals, both of which can limit lipid peroxidation
- Resveratrol (0-20  $\mu\text{M}$ ) showed concentration-dependent anti-inflammatory activities (as shown by suppressing IL-6 and iNOS mRNA levels) (Ma et al 2002)
- Resveratrol can activate Nuclear factor (erythroid-derived 2)-like 2 (Nrf2), and Nuclear factor kappa B (NF-KB), both of which are thought to have cytoprotective effects in vivo
- Resveratrol can activate Silent Regulator 2/sirtuin 1 (SIRT-1), a NAD-dependent acetylase, through the action of adenosine monophosphate activated protein kinase (AMPK)

# Pharmacology: Impaired glucose tolerance



Mechanistic in vivo animal studies of type 2 diabetes models suggest that resveratrol (doses ranging from 10-100 mg orally):

- increases insulin secretion
- improves glucose tolerance
- improves pancreatic islet structure and function
- decreases insulin resistance, creatinine levels, urea clearance, and proteinuria
- decreases oxidative damage



Direct and indirect effects whereby resveratrol improves insulin secretion from pancreatic islets of animals with experimental type 2 diabetes. RSV = resveratrol, ROS = reactive oxygen species, UCP2 = uncoupling protein 2. (Graph from Szkudelski and Szkudelska, 2015)

## Pharmacology: Pain



- Use of polyphenols such as resveratrol attenuated neuropathic and nociceptive pain in animals
- Supplementation of resveratrol in several in vivo animal models of diabetes (10 and 20 mg intraperitoneal injection in rats; 5-20 mg orally in mice) reduced hyperalgesia, decreased serum TNF- $\alpha$  levels and whole brain nitric oxide release
- A gel formulation containing 0.025% resveratrol reduced inflammation and edema in an in vivo rat model of pain when measured 1-4 hours post injury

## Nonclinical Pharmacokinetics



- Resveratrol is detectable in plasma within 15 minutes of oral administration, and reaches peak concentration within 30 minutes; the elimination half-life is between 8-12 hours
- Highest distribution is found in liver, followed by the pituitary gland, muscle, stomach, intestines, and the optic nerve
- Resveratrol undergoes extensive conjugation during its metabolism, does not accumulate over time and is largely eliminated via the feces
- Similar metabolic profiles were reported for topical and oral routes of administration

# Clinical Pharmacokinetics



- Resveratrol is highly absorbed ( $\approx 70\%$ ) but has low absolute bioavailability after oral administration due to extensive first pass metabolism
- In a single dose study of 500 mg, 1.0 gram, 2.5 gram, and 5 gram
  - $C_{\max}$  values range from 73 ng/ml to 539 ng/ml (after the 1st dose)
  - $T_{\max}$  ranged from 0.8 to 1.5 hours
  - Six metabolites identified include 2 monosulfates, 1 disulfate, 2 monoglucuronides, and 1 glucuronide-sulfate products suggesting primarily phase II metabolism
  - $t_{1/2}$  ranged from 3-8 hours
- In a multi-dose study of 25, 50, 100, and 150 mg every 4 hours for 13 doses
  - $C_{\max}$  values ranged from 1.48 ng/ml to 24.8 ng/ml (after the 1st dose)
  - $C_{\max}$  values ranged from 6.9 ng/ml to 63.8 ng/ml (after the 13th dose)
- The volume of distribution is approximately 1.8 L/kg
- Circulating human blood levels are lower than resveratrol concentrations found to be active in vitro and ex vivo



## Clinical Pharmacokinetics (2)



- In a separate multi-dose small study of 12 subjects, there was no difference in the PK profile between young (20-40) and older (>65) subjects and males compared to females
- Application of resveratrol (500 ug in 10ul/cm<sup>2</sup>) for 24 hours to ventral forearms (n=6 women without skin disorders) showed high variability in absorption (by the tape stripping method); most of the applied product remained in the stratum corneum layers of the skin
- Orally administered resveratrol (1 gram/day) for 4 weeks inhibited cytochrome P450 enzymes (CYP450) 3A4, 2D6, and 2C9; for drugs metabolized by these CYP450, concomitant resveratrol may lead to increased blood levels and longer elimination half life ( $t_{1/2}$ )

# Nonclinical Safety



- Resveratrol was non-irritating to skin and eyes and was non-sensitizing when topically applied in animal models
- Toxicities were dose- and formulation- related:
  - some studies reported no toxic effects
  - some studies reported adverse clinical signs, dose related increase in nephrotoxicity in several species (mouse, rat, dog, and rabbit) in 4-week, 13-week, and 6-month toxicity studies
- Gastrointestinal (diarrhea, loose stool) and urinary bladder (epithelial hyperplasia) effects were reported for some resveratrol formulations

## Nonclinical Safety: Genotoxicity



- Trans-resveratrol was non-mutagenic in several Ames assays
- Positive clastogenic activity in a chromosomal aberration test in human lymphocytes (both in the presence or absence of metabolic activation)
- Negative genotoxic activity in the *in vivo* bone marrow micronucleus test in rats

## Other Nonclinical Safety



- Developmental and reproductive toxicity:
  - Resveratrol binds to estrogen receptor
  - No *in vivo* adverse effects were reported
  - No adverse reproductive or fetal effects were seen in embryofetal toxicity studies in rats
- Carcinogenicity
  - Resveratrol was not associated with an increase in benign or malignant tumors in a 6-month transgenic mouse model study
  - Dose-related increase in death, likely due to accumulation of resveratrol in GI tract (2000 and 4000 mg/kg/day orally)

## Adverse Events: FAERS Data



- FDA Adverse Event Reporting System (FAERS) database (August 9, 2017):
  - 7 cases were found
  - None described the use of resveratrol as part of a compounded product
  - Reported AEs while using resveratrol included gynecomastia, decreased effectiveness of an analgesic, interstitial nephritis and persistent vomiting and diarrhea leading to acute pre-renal failure, Hodgkin's lymphoma, multiple myeloma, and depression
    - It was difficult to assess causality because of a lack of information or confounding by disease and the use of multiple concomitant medications or supplements
    - The case of gynecomastia involved a 15 year old male taking risperidone and resveratrol (dose unknown, 4 times per day); risperidone can cause gynecomastia
      - Risperidone is metabolized by CYP450 2C9
      - Resveratrol inhibits CYP450 2C9; insufficient information was provided to assess a possible drug-drug interaction

# Adverse Events: CAERS Data



- Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS) database (August 17, 2017):
  - 377 reports were identified
  - In most cases, multiple dietary supplements were being ingested; some cases suggest a role for resveratrol in adverse events
  - A conclusion regarding the role of resveratrol in adverse findings cannot be drawn

# Clinical Safety



- Adverse events are primarily mild to moderate gastrointestinal symptoms including diarrhea, abdominal pain, flatulence, nausea, and heartburn
- Phase 2 trial in myeloma patients (n= 24) reported nausea, diarrhea, vomiting, fatigue, and renal failure (5 cases – possibly due to dehydration from gastrointestinal effects)
- Patients with nonalcoholic fatty liver disease (n= 10) had increased frequency of loose stools and mildly increased alanine and aspartate aminotransferases
- Some organizations recommend that resveratrol supplementation should be avoided in women with hormone sensitive conditions (e.g., breast, uterine, ovarian cancer, endometriosis, uterine fibroids)

# Safety Conclusion



- Animal models show the kidney, gastrointestinal, and urinary bladder as target organs of toxicity
- In humans, adverse events include primarily gastrointestinal symptoms across studies
- In clinical adverse event reports, concomitant therapies and/or underlying diseases makes it difficult to make any conclusion about attribution to resveratrol



## Effectiveness in Impaired Glucose Tolerance



- Impaired glucose tolerance (IGT) is not a recognized disease; it is a risk marker for future diabetes.
- Delaying the onset of diabetes in patients with IGT has not been shown to offer any micro or macro-vascular benefits to patients in long term randomized controlled trials.
- A clinical trial (4 week open label) was identified in patients (n=10; > 64 years of age) with impaired glucose tolerance; resveratrol was administered in divided doses (1.0, 1.5, or 2.0 grams/day)
  - Results:
    - Fasting blood sugar was unchanged
    - Decrease in peak post-meal glucose and 3-hour glucose AUC
    - Decrease in post meal insulin level
    - Insulin sensitivity improved in one of two scales
    - Insulin secretion and disposition index did not change significantly
    - Subtle changes in diet and exercise could have contributed to the observed results

## Effectiveness in Pain



- No clinical trials, either by oral or topical routes of administration, were identified where resveratrol alone was used for the treatment of pain
- A small open label study where Brazilian women (n=12) with dysmenorrhea and pelvic pain related to endometriosis were treated with resveratrol after treatment with contraceptive medications
  - Patients treated initially with drospirenone 3 mg and ethinylestradiol 30 ug for 6 months
  - Resveratrol 30 mg added at six months because patients were not completely pain free
  - Pain was significantly relieved with contraceptives (using a categorical pain scale of 0 to 3)
  - After 2 months of resveratrol treatment, there were significant improvements in pain scores
  - This is a small, open label, uncontrolled study using an unvalidated pain scale that does not support clinical effectiveness

## Effectiveness Conclusion



- IGT is a risk marker for the development of diabetes; the benefit of treatment of IGT is unclear
  - for impaired glucose tolerance, the mainstay of treatment is an intensive behavioral life-style intervention program to achieve and maintain at least a 7% weight loss during the first 6 months of intervention and increase physical activity to at least 150 minutes per week
- Found only one study evaluating the effect of resveratrol in the treatment of IGT but it is insufficient to support effectiveness
- Resveratrol has not been adequately studied for the treatment of pain

# Historical Use in Compounding



- Resveratrol was first identified from the roots of white hellebore (*Veratrum grandiflorum*) in 1940
- Resveratrol is available as a dietary supplement
- Insufficient information is available to determine how long resveratrol has been used in pharmacy compounding
  - Between 2011 to 2015: “The Postal Inspector General provided data which show payments for over 5,000 prescriptions for resveratrol totaling more than \$16 million” and also note that “resveratrol is a dietary supplement which has been prescribed for use in compounded drug creams for back pain.” Letter from Scott and Cummings to the notice in the Federal Register (81 Fed. Reg. 61255)

## Summary



- Trans-resveratrol is well characterized
- Safety concerns are primarily related to gastrointestinal adverse effects observed in clinical studies and possible drug interactions related to inhibition to cytochrome P450 enzymes; nonclinical data suggest the kidney, gastrointestinal, and urinary bladder to be target organs of toxicity
- Clinical effectiveness has not been established
  - There is limited data in patients with impaired glucose tolerance and pain
  - There is poor absolute bioavailability due to extensive gut and liver metabolism
- History of compounding is limited; available orally as dietary supplement.

## Recommendation



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





# Liposome Drug Products

Pharmacy Compounding Advisory Committee Meeting  
November 21, 2017

**Katherine Tyner, PhD**

Associate Director for Science (Acting)

Office of Pharmaceutical Quality

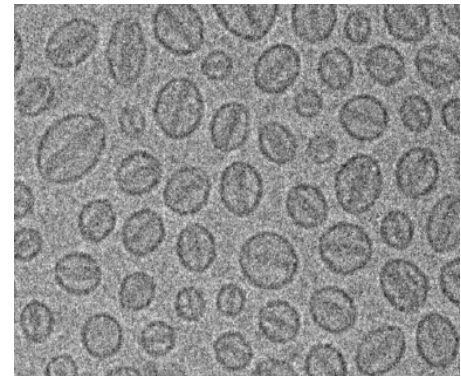
Center for Drug Evaluation and Research



# Overview of Presentation



- Liposome drug product background
- Evaluation criteria used in developing a recommendation as to whether drug products or categories of drug products present demonstrable difficulties for compounding that reasonably demonstrate and are reasonably likely to lead to an adverse effect on the safety and/or effectiveness of the drug product or category of drug products\*
  - Complex formulation
  - Complex drug delivery mechanism
  - Complex dosage form
  - Complex characterization and control of drug bioavailability
  - Complex compounding process
  - Complex physicochemical or analytical testing
- Risks and benefits to patients of compounded liposome drug products
- Recommendation



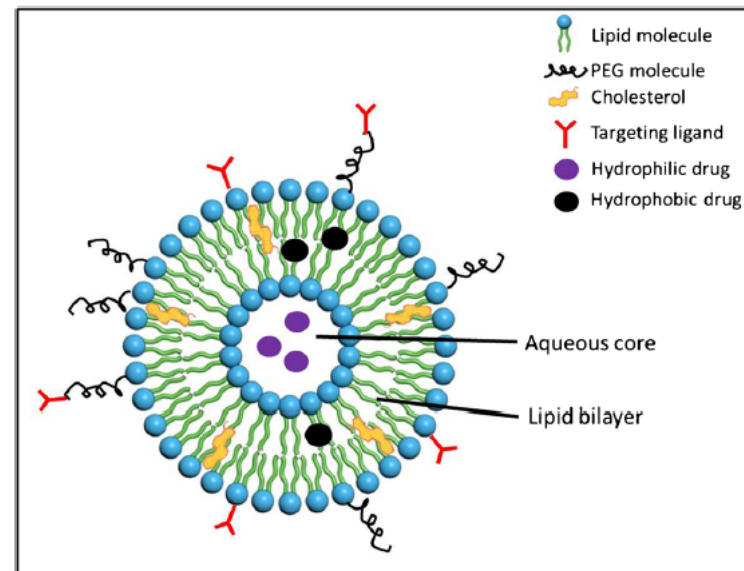
[www.fda.gov](http://www.fda.gov)

\* The analyses of the complexity of the formulation, drug delivery mechanism, dosage form, bioavailability issues, compounding process, and physicochemical or analytical testing issues are solely for purposes of determining whether drug products that are the subject of this consult are difficult to compound under sections 503A and 503B.

# Liposome Drug Product Background



- Liposome: microvesicle composed of a bilayer and/or a concentric series of multiple bilayers separated by aqueous compartments formed by amphipathic molecules such as phospholipids that enclose a central aqueous compartment
- Liposome Drug Product: a drug product in which the active pharmaceutical ingredient (API) is contained in liposomes
  - For this review, the category also includes products in which the API is intended to be contained in liposomes



Draft Guidance for Industry. Liposome drug products, chemistry, manufacturing, and controls; human pharmacokinetics and bioavailability; and labeling documentation. U.S. Food and Drug Administration.

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070570.pdf> (2015)

## Liposome Drug Product Background (2)



- Structurally, liposomes are composed predominantly of phospholipids arranged in a bilayer configuration (termed lamellar)
- Size of liposomes ranges from 20 nm to greater than 1000 nm
  - Products that involve the application of nanotechnology are discussed within the Agency's guidance on nanotechnology
  - Liposome Drug Products are among the most common approved drug products containing nanomaterials
- Modification of surface characteristics (e.g., through lipid components and composition) can impact circulation times and targeted delivery of liposomes

Kapoor M, Lee SL, Tyner KM. AAPS J. 2017. DOI: 10.1208/s12248-017-0049-9; D'Mello SR, Cruz CN, Chen ML, Kapoor M, Lee SL, Tyner KM. Nature Nanotechnology. DOI: 10.1038/NNANO.2017.67; Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology (2014). <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM401695.pdf>

# Liposome Drug Product Background (3)



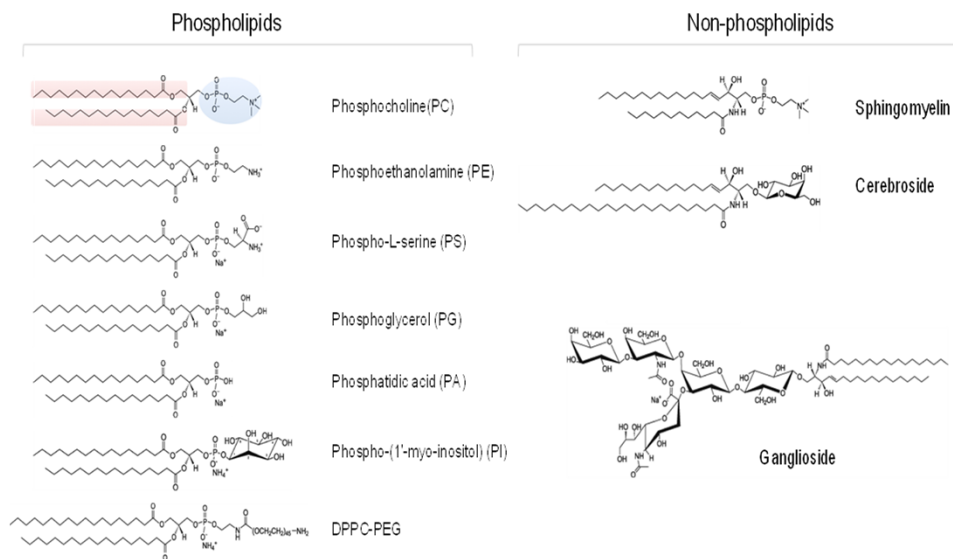
- First FDA approval in 1995
- There are 11 FDA approved drug products containing liposomes
  - Administered by intravenous, epidural, or intrathecal injection
  - Indications include the treatment of ovarian cancer, certain fungal infections, age-related macular degeneration, and pain
- Versatile nature capable of entrapping both hydrophilic and hydrophobic APIs
- Commonly used to alter the biodistribution of an API
  - Can improve drug dissolution, stability, deliverability, biodistribution, and bioavailability

Trade name	Active Ingredient	Indication	Route	Initial Approval Date
Doxil	Doxorubicin HCl	Ovarian cancer, AIDS-related Kaposi's sarcoma, multiple myeloma	Intravenous	11/17/1995
DaunoXome	Daunorubicin Citrate	Advanced HIV-related Kaposi's sarcoma (relapse)	Intravenous	4/8/1996
AmBisome	Amphotericin B	Certain fungal infections	Intravenous	08/11/1997
DepoCyt	Cytarabine	Lymphomatous meningitis	Intrathecal	04/01/1999
Visudyne	Verteporfin	Photosensitizer for treatment of certain patients	Intravenous	04/12/2000
Definity	Perflutren	Ultrasound contrast agent for use in certain patients	Intravenous	07/31/2001
DepoDur	Morphine Sulfate	Opioid local analgesic	Epidural	05/18/2004
Exparel	Bupivacaine	Postsurgical analgesia	Intravenous	10/28/2011
Marqibo	Vincristine Sulfate	Acute lymphoblastic leukemia	Intravenous	08/09/2012
Onivyde	Irinotecan HCl	Metastatic pancreatic cancer	Intravenous	10/22/2015
Vyxeo	Daunorubicin and Cytarabine	Therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)	Intravenous	08/03/2017

# Liposome Drug Products Have Complex Formulations



- Factors that are known to demonstrate formulation complexity and their impact on product performance include:
  - Lipid attributes
  - Other inactive ingredient attributes
  - Liposome stability

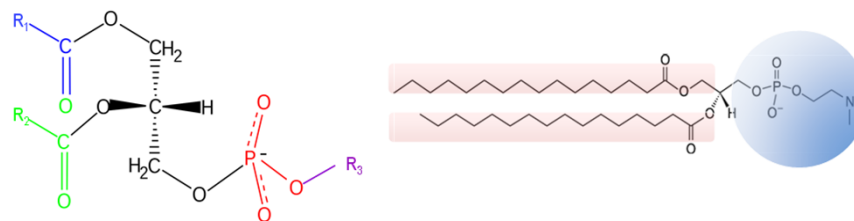


# Liposome Drug Products Have Complex Formulations (2) — Lipid Attributes



- Structure of lipid can impact lipid function and stability

- Hydrophilic head group
  - Can impact liposome-membrane interaction and drug permeation
- Hydrophobic tail
  - Can impact stability
- Linker
  - E.g., ether vs. ester
  - Can impact stability and biodegradability



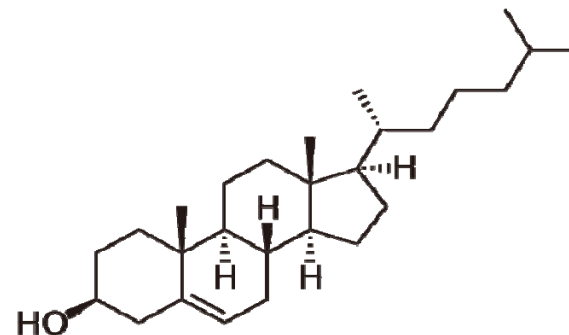
- Can impact safety

- Double-tailed lipids, when becoming single-tailed due to chemical degradation, may form lysolipids
- Lysolipids may bind to red blood cell membranes and cause hemolysis and/or perturb the cell membrane integrity

# Liposome Drug Products Have Complex Formulations (3) — Other Inactive Ingredients



- Liposomes often contain cholesterol (reduces drug leakage) and polyethylene glycol (PEG) or PEG derivatives (promote longer circulation times)
- The concentration range of lipids (as inactive ingredients) and relative ratio of these inactive ingredients within a liposome, are critical factors that affect the safety, effectiveness, and stability of a liposome drug product. In addition, the grade of lipids may also significantly impact the product quality and performance.
  - Can impact the pharmacokinetic/pharmacodynamic performance of the product



## Liposome Drug Products Have Complex Formulations (4) — Stability



- The physical and chemical stability of liposome drug products can be affected by a number of formulation-related factors
  - e.g., the size and size distribution of the lipid vesicles, morphology, surface coating, pH, buffer, or counter ions
- Structural integrity of liposomes could be compromised due to
  - Lipid fusion (i.e., irreversible coalition of smaller liposomes to form larger liposomes)
  - Aggregation (i.e., reversible conglomeration or pooling of two or more liposomes without fusion)
  - Leakage of the contained API during storage



## Liposome Drug Products Have Complex Formulations (5) -- Conclusion



- Selection of lipids for formulating liposomes impacts the finished product quality, safety, and performance
- Other inactive ingredients impact the physicochemical properties of the liposome drug product, which in turn impact its pharmacokinetic/pharmacodynamic (PK/PD) profile/behavior
- Formulation related factors impact physical and chemical stability of liposome drug products

**The complexity of liposome drug product formulations presents demonstrable difficulties for compounding**

# Liposome Drug Products Have Complex Drug Delivery Mechanisms



- To achieve proper performance, liposome drug products need to be designed to release the API contained in the liposome in a predictable manner and are expected to remain stable throughout the intended shelf-life as well as under in-use conditions
  - E.g., prevent off-target premature drug release in systemic circulation after administration
- Different delivery profiles and delivery mechanisms can be achieved by selection of different lipids and an appropriate production process
- Factors that are known to have a substantial impact on the complex nature of the drug delivery mechanism include:
  - Interactions between the liposomes and the body
  - Physicochemical properties (including size and internal environment)
  - Lipid composition
- **This complexity applies to all routes of administration**

# Liposome Drug Products Have Complex Drug Delivery Mechanisms (2) – Liposome-Blood Component Interactions



- Ensuring predictable drug delivery with liposome drug products depends on a balance of interactions between the liposome carrier system and blood components
  - Lipid proteins and opsonins
- Opsonization may also be altered by modulating the composition, size, and surface characteristics of the liposome
- The interactions can facilitate delivery of the API, but if not controlled, it may lead to undesired release of the API
  - Liposome drug products generally incorporate a higher dose of API than traditional dosage forms
  - Undesired API release such as “dose dumping” can lead to exposure at a toxic level

## Liposome Drug Products Have Complex Drug Delivery Mechanisms (3) – Other Factors

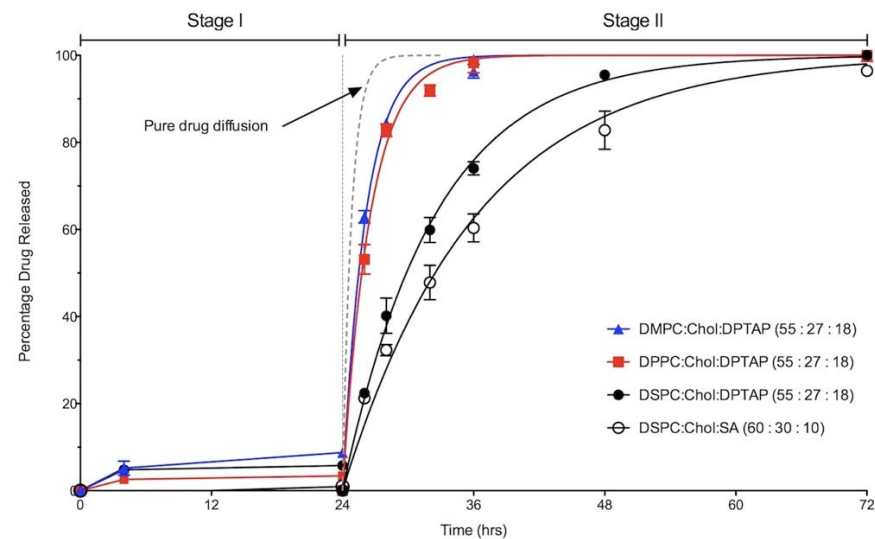


- The rate of in vivo release depends on the API's
  - Physicochemical properties
  - Loading mechanisms
  - Location and state of entrapped drug
  - Lipid composition
  - Liposome internal environment
    - e.g. internal pH and buffer concentration

# Liposome Drug Products Have Complex Drug Delivery Mechanisms (4) – Conclusion



- The mechanism by which an API is released from a liposome drug product involves precisely designing and formulating a system that delivers a specific amount of API per unit time and, in most cases, in a specific region
- *In vivo* biodistribution and release characteristics are affected by several factors (e.g. physicochemical properties of the final product)



**The complexity of the drug delivery mechanisms of liposome drug products presents demonstrable difficulties for compounding**

X. Xu, M.A. Khan, and D. J. Burgess. International Journal of Pharmaceutics (2012) DOI:10.1016/j.ijpharm.2012.01.030

# Liposome Drug Products Are Complex Dosage Forms



- Liposome drug product dosage forms are suspensions or lyophilized powders for suspension
- Characteristics of the physical dosage units of liposome suspensions or lyophilized powders for suspension that are difficult to consistently achieve or maintain include:
  - Well-defined and controlled particle size and particle size distribution
  - Status of the API (e.g., whether it is contained within the liposome)
  - Surface chemistry of the liposomes
- These characteristics have a significant impact on the safety and effectiveness of liposome drug products
- Various formulation components, including inactive ingredients, play a critical role in dosage form performance and stability
  - Such components can vary for different drug products that have different routes of administration
- Extensive product development and precise control over raw material and optimization of the process parameters are essential to produce safe, effective, and high-quality liposome drug products

**The complexity of the dosage form of liposome drug products presents demonstrable difficulties for compounding**

# Bioavailability of Liposome Drug Products is Difficult to Characterize and Control



- The plasma clearance of the liposome drug product occurs as a combination of several processes with different elimination rates
  - Tissue uptake of the liposome drug product
  - API leakage from the liposomes
  - Clearance of released and unbound API
  - Clearance of the liposome drug product
  - Clearance of the drug carrier
- Different API forms may have different ADME (absorption, distribution, metabolism, elimination) and the difficulty in determining the amount of various forms of API makes it complex to characterize and control bioavailability
  - Interactions between blood proteins and lipoproteins may affect API release and pharmacological properties of a liposome drug product in vivo. Such interactions can have safety implications because of “dose dumping.”
- Because of the complexity of the interaction between API release from the liposomes and tissue uptake of the API, a simple measurement of total API may not be reflective of the bioavailability of the API at the intended target (i.e., site of action)

## Bioavailability of Liposome Drug Products is Difficult to Characterize and Control (2)



- Biodistribution and release of API may be impacted by subtle changes to
  - Formulation composition
  - Purity of lipid as raw material
  - Manufacturing processes
- Influence the availability of an API in systemic circulation, at tissue or sub-cellular targets

**Characterizing and controlling the bioavailability of liposome drug products is complex and presents a demonstrable difficulty for compounding**



# Liposome Drug Products Have Complex Compounding Processes



- The production process for a liposome drug product generally involves the following steps:
  - Formation of liposomes
    - Temperature of aqueous phase influences liposome particle size and size distribution
  - Size reduction
    - Speed, time, and temperature during homogenization influence mean liposome particle size which, in turn, can alter product performance
  - Loading of API(s)
    - Temperatures during the API loading process impact encapsulation and loading efficiency
  - Purification
    - It is critical that any employed purification procedure(s) do not adversely impact the quality and performance of the liposome drug product

Kapoor M, Lee SL, Tyner KM. AAPS J. 2017. DOI: 10.1208/s12248-017-0049-9

Manufacturing method	Manufacturing step <sup>a</sup>	In-process controls
Passive loading	Hydration of thin lipid film	Visual inspection for complete lipid dissolution, residual solvents, lamellarity, pH
	Ethanol injection	Visual inspection for clarity, lamellarity, pH
	Homogenization/extrusion	Particle size, PSD, extrusion membrane integrity, lamellarity, assay, individual lipid composition change
	Diafiltration	Solvent content, particle size, PSD, filter integrity, % drug encapsulation, % free drug, pH, individual lipid composition change
	Aseptic filtration	Bioburden, filter integrity, pH, lamellarity, individual lipid composition change
	Lyophilization	Fill weight and moisture content of final powder
Capping and sealing	Visual inspection, fill weight test, leak test, release testing (including sterility)	
Active loading	Concentration adjustment post drug loading	Particle size, PSD, % drug encapsulation, % free drug, assay, pH
Active loading before administration	After mixing empty liposomes with drug solution	Release testing (particle size, PSD, % drug encapsulation, % free drug, assay, pH, residual solvents, heavy metals, osmolality, lamellarity)
Double emulsion	First emulsification	Particle size, PSD, bioburden, conductivity
	Second emulsification	Free drug, particle size, PSD, pH

<sup>a</sup>PSD particle size distribution  
<sup>a</sup>Some steps in passive loading are also applicable to other manufacturing processes

# Liposome Drug Products Have Complex Compounding Processes (2)



- Quality of the produced liposome drug products are highly dependent on the process parameters including:
  - Extrusion membrane pore size
  - Extrusion/microfluidization pressure
  - Temperature
  - Extrusion cycles
- Freshly prepared API-containing liposomes always contain some unencapsulated API, which may cause liposome stability issues during storage due to API-liposome interactions at the surface (e.g., charge-charge interactions)
  - Unencapsulated API may result in unwanted systemic toxicity upon administration to patients because of high API exposure
  - Filtration and/or dialysis methods are commonly used to remove unencapsulated API
- Quality of the liposomes may also be impacted by change in manufacturing scale; manufacturing process parameters that may be altered in scale-up and may affect performance include:
  - Shear
  - Pressure
  - Temperature
  - Batch-size-related hold times
  - Lyophilization parameters

## Liposome Drug Products Have Complex Compounding Processes (3)



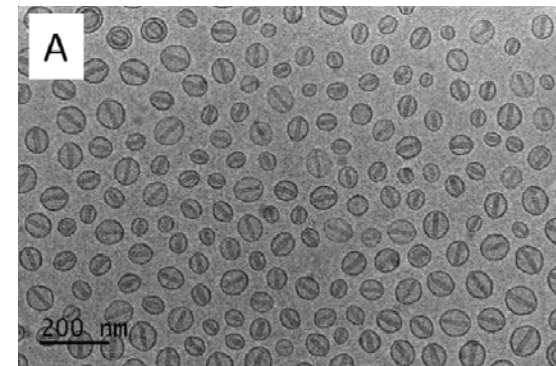
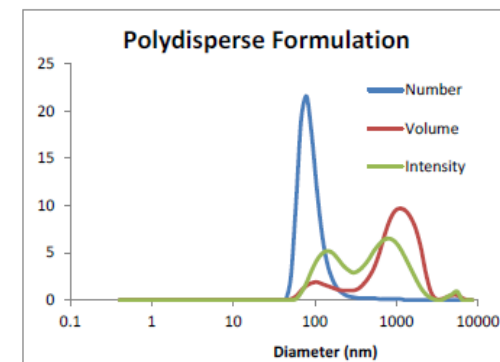
- Poor control over unit operations may lead to variability in product quality, which may potentially lead to a negative impact on product efficacy and safety

**Producing liposome drug products involves complex compounding processes that present demonstrable difficulties for compounding**

# Liposome Drug Products Involve Complex Physicochemical Testing



- Particle size is a critical quality attribute for liposome drug products
  - Impacts ADME, stability, drug release, etc.
- Liposome particle size and size distribution impact biodistribution and drug pharmacokinetics and are often critical determinants of drug product efficacy and safety
- Parameters used for reporting particle size may vary based on the technique used and the instrument parameters
- Oftentimes, the sample preparation procedure itself has great influence on the measurement results which may or may not be properly captured in the test report
- In addition, multiple techniques, such as dynamic light scattering (DLS) and electron microscopy (EM), are usually recommended to thoroughly characterize particle size and size distribution



# Liposome Drug Products Involve Complex Physicochemical Testing (2)

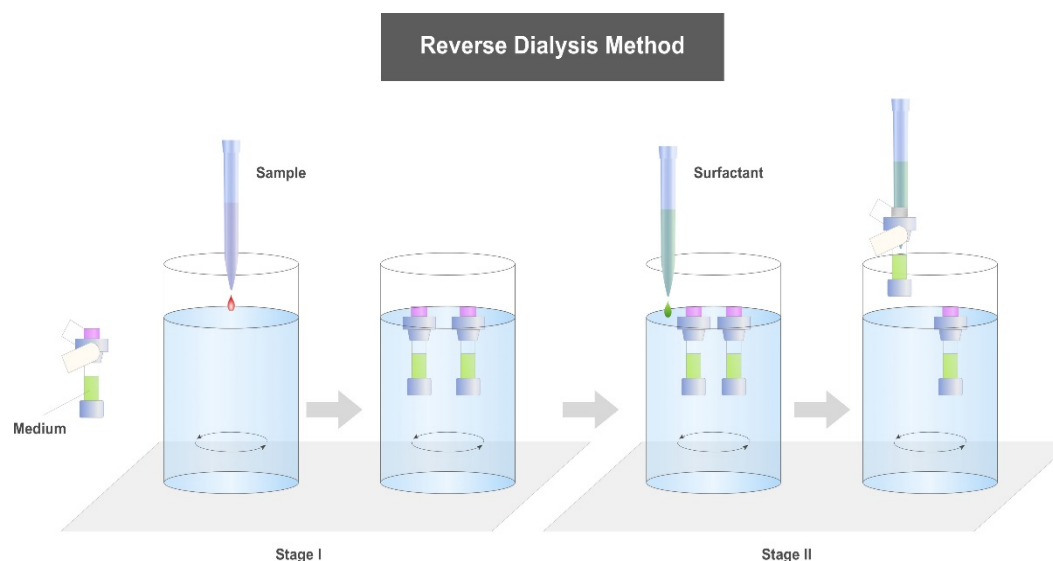


- Lipids are considered critical raw materials for liposome drug product manufacturing as they may impact the quality and performance of liposome drug products
  - Detailed information, such as manufacturing, characterization, and control of lipids should be known
  - Specifications for a lipid may include, but are not limited to, source, physicochemical characteristics, and degradants (especially lysophospholipid)
- With respect to lipid degradants, complete degradation profiles of liposome drug products are needed to accurately determine potential safety risks of the product
  - Lysolipid content is a critical attribute to monitor and control due to the associated toxicity issues (hemolysis and/or apoptosis)
  - Lysolipid content should be monitored and controlled through in-process and shelf-life product testing

# Liposome Drug Products Involve Complex Physicochemical Testing (3)



- Liposome drug product characterization should include an *in vitro* test for release of API from the liposomes
  - Used to evaluate product quality, suitability of in-process controls during manufacturing, and influence of chemistry, manufacturing, and controls (CMC) changes on product quality
- The *in vitro* release method should be able to discriminate between acceptable and non-acceptable batches of the drug product



# Liposome Drug Products Involve Complex Physicochemical Testing (4)



- Additional complex physicochemical testing for various attributes of liposome drug products includes:
  - Morphology of the liposome, including lamellarity determination, if applicable
  - Surface characteristics, as applicable
  - Liposome structure and integrity
  - Parameters of the contained drug (e.g., drug encapsulation efficiency)
  - Liposome drug loading
  - Leakage rate of drug from the liposomes throughout the product's shelf life
  - Liposome integrity changes (e.g., release, containment efficiency, size) in response to changes in salt concentration
  - Spectroscopic data to support the liposome structure (e.g., phosphorus nuclear magnetic resonance)

## Liposome Drug Products Involve Complex Physicochemical Testing (5)



- Suitable analytical methods need be employed to properly characterize liposome drug products, which can often be difficult given the complexity of liposome drug product formulations
- Use of inappropriate methods could produce false results, thereby calling into question data reliability and, hence, product quality

**The physicochemical and analytical testing for liposome drug products is complex and presents demonstrable difficulties for compounding**



# Risks and Benefits to Patients of Compounded Liposome Drug Products



- Compounded drugs are not FDA-approved, but they can serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product
- Liposome drug products present a significant safety risk for compounding given the complexities described
  - Many of the APIs used in liposome drug products are cytotoxic
  - If the API is not encapsulated properly or is released prematurely, the product may be potentially ineffective or hazardous

**The risks to patient safety of compounded liposome drug products outweigh any potential benefit of increased patient access**

## Recommendation



- Liposome drug products present demonstrable difficulties for compounding that reasonably demonstrate, and are reasonably likely to lead to an adverse effect on the safety and effectiveness of such products
- Taking into account the risks and benefits to patients, we believe that liposome drug products should be included in the Difficult to Compound List under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act





# **Drug Products Produced Using Hot Melt Extrusion (HME)**

Pharmacy Compounding Advisory Committee Meeting  
November 21, 2017

**Celia N. Cruz, PhD**

Division Director (acting)  
Office of Testing and Research  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

# Overview Of Presentation



- HME background
- Evaluation criteria considered in formulating a recommendation as to whether drug products produced using Hot Melt Extrusion (**HME**) present demonstrable difficulties for compounding that reasonably demonstrate and are reasonably likely to lead to an adverse effect on their safety or effectiveness
- Risks and benefits to patients
- Recommendation

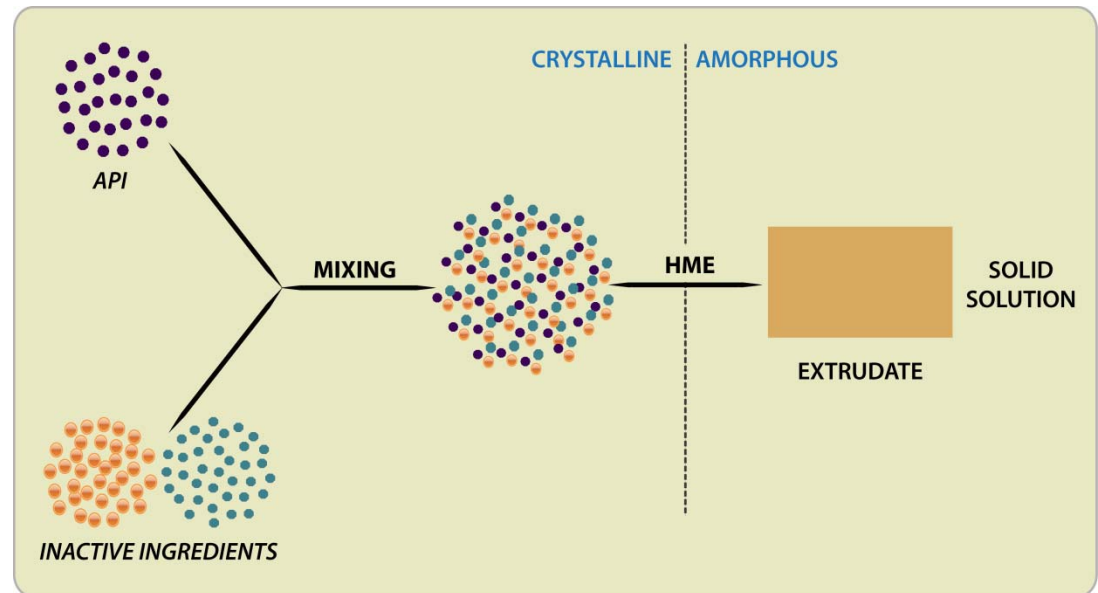
The analyses of the complexity of the formulation, drug delivery mechanism, dosage form, bioavailability issues, compounding process, and physicochemical or analytical testing issues are solely for purposes of determining whether drugs that are the subject of this consult are difficult to compound under sections 503A and 503B.

[www.fda.gov](http://www.fda.gov)

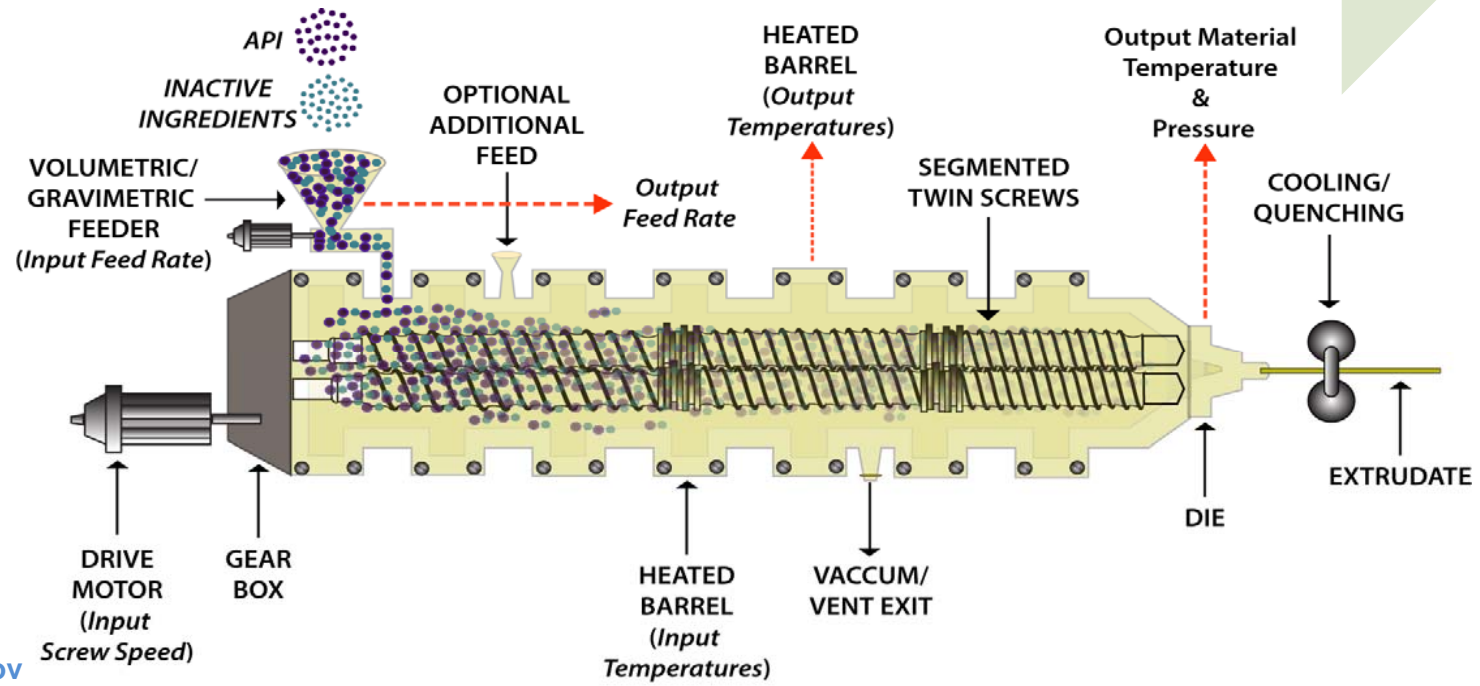
# HME Background

For the purposes of this presentation and our review, FDA defines HME as a continuous process operation that achieves, or is intended to achieve, the molecular mixing of active pharmaceutical ingredients (APIs) and inactive ingredients (e.g., polymers) at temperatures above their glass transition temperatures ( $T_g$ ) and/or melting temperatures ( $T_m$ ) within an extruder.

The objective of an HME process is to enhance the solubility of poorly water-soluble drugs by converting the formulation components into an amorphous phase (non crystalline) product with uniform content, referred to as the “extrudate.”



# HME Background (2)





## HME Background (3)

In an HME process, a mixture of API and inactive ingredients (e.g., polymers) is continuously fed from the hopper into an extruder. The barrel and screws in the transport section simultaneously mix, heat, and convey the material.

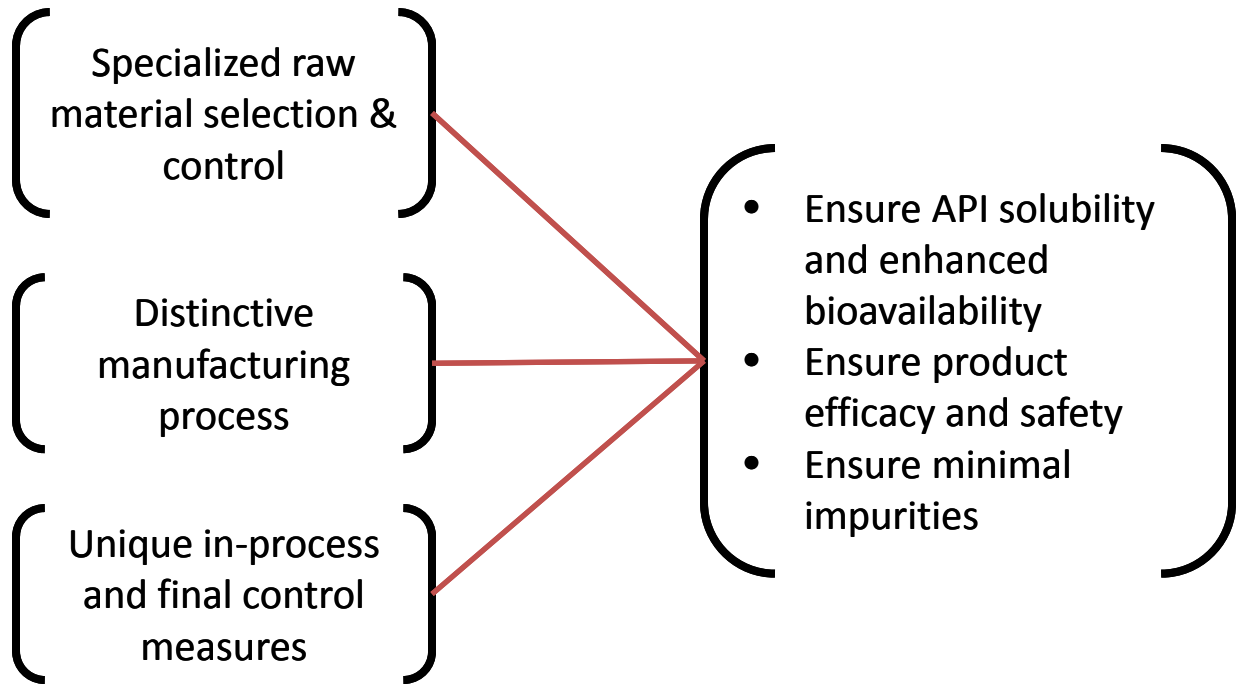
Heat and shear are applied to melt the ingredients and force the mixture through an orifice. The die at the end of the extruder gives a desired shape to the extrudate.

The extrudate is then cooled for further processing into a finished dosage form.

The temperature profile within the extruder's barrel, the screw configuration, and speed are optimized and maintained for proper conveying and mixing, without thermally degrading the materials.



# HME Complexity Overview



# Difficult to Compound Analysis



Evaluation criteria considered in formulating a recommendation as to whether drug products produced using **H**ot **M**elt **E**xtrusion (**HME**) present demonstrable difficulties for compounding that reasonably demonstrate and are reasonably likely to lead to an adverse effect on their safety or effectiveness:

- Complex formulation
- Complex drug delivery mechanism
- Complex dosage form
- Complex characterization and control of bioavailability
- Complex compounding processes
- Complex physicochemical or analytical testing

## Drug Products Produced Using HME Have Complex Formulations



- Selection of API and inactive ingredients is difficult due to limitations on API and inactive ingredients that will result in a stable amorphous phase when extruded.
- The critical quality attribute of the extrudate is a single amorphous phase, or solid solution, in order to ensure uniformity, performance and stability of the drug product.
- To maintain quality in drug products produced using HME, the extrudate must maintain its amorphous state (i.e., not recrystallize) after production, during storage, and upon release *in vivo*.
- Formulation selection is difficult as components should be carefully chosen to ensure that the extrudate is uniform, amorphous, and stable.

# Drug Products Produced Using HME Have Complex Formulations (2)



## Active Ingredient Thermal Properties

- HME process conditions require the API to be thermally stable and maintain its chemical stability during the process and during storage in order to achieve proper performance.
- A failure to understand the limitations of API performance under temperature and shear conditions could lead to improper extrusion conditions, generation of impurities, and lack of compatibility of the API and inactive ingredients.
- The melting point of the API should be within acceptable ranges in order to prevent thermal degradation and avoid thermal impurities.
- As noted above, one of the main objectives of using an HME process is to increase bioavailability of poorly soluble drugs by producing an amorphous API form.
  - However, amorphous products are less thermodynamically stable compared to crystalline products.
- It is essential to monitor the T<sub>g</sub> of the extrudate containing the API under various temperature and humidity conditions.

# Drug Products Produced Using HME Have Complex Formulations (3)



## Active Ingredient Solubility

- Two types of API solubility are important when processing using HME:
  - API solubility in water for both the crystalline and amorphous forms (improving bioavailability)
  - Solubility of the API in the polymer matrix (solid in solid solubility) - formation of solid solution
- The HME process increases API solubility by converting it to its amorphous state. Therefore, understanding this change in API solubility is important to predict its release and bioavailability.
- If the solubility of the API in the polymer carrier is increased, it may result in the formation of a solid solution. Partially miscible components may lead to a solid particulate dispersion extrudate, where the API is only partly dispersed and potentially crystalline, and a physical mixture of API and polymer carrier may exist.
- Establishing the solubility limit (i.e., max API to polymer ratio) for the formulation, which requires pre-formulation physical characterization of ingredients, is critical to achieving proper product performance.

# Drug Products Produced Using HME Have Complex Formulations (4)



## Active Ingredient Polymorph

- HME process converts the API from a crystalline to amorphous state, and this conversion is critical for achieving enhancements in solubility and bioavailability.
- API entering the extruder can exhibit multiple crystalline forms. The properties of these polymorphs should be known and considered when operating the extruder for proper conversion to an amorphous state.
- Detecting and determining different polymorphic forms of the API and the thermal transitions that can occur upon heating can be difficult, requiring interpretation of calorimetry studies.
- Some APIs may exhibit thermally induced polymorphism and convert into a different polymorph at a higher temperature instead of melting, potentially resulting in crystalline API of different solubility in the extrudate.

# Drug Products Produced Using HME Have Complex Formulations (5)



## Active Ingredient Purity

- Purity of API is critical to the safety and effectiveness of drug products produced using HME.
- Presence of degradants, solvents, or other process impurities within the API may influence the performance characteristics of the extrudate and final product.
- Degradants may increase during heat processing and storage, potentially impacting safety of the product; impurities and solvents can impact the process efficiency, resulting in inadequate melting.
- Interactions between API and impurities (e.g., thermal impurities and residual solvents) during melting and quenching should be analyzed through accelerated stability studies on the extrudate because of their effect on HME product performance.

# Drug Products Produced Using HME Have Complex Formulations (6)



## Inactive Ingredients: *API carriers*

- Drug products produced using HME contain API embedded in a carrier (or matrix) system.
  - May function as thermal binders, drug stabilizers, drug solubilizers, or drug-release controlling inactive ingredients. Carriers can be polymeric or non-polymeric, but are mostly the former.
  - Polymers should exhibit appropriate thermoplastic characteristics, be thermally stable at extrusion temperatures, and be safe for use.
  - Carriers should be able to be processed at relatively lower temperatures (have low Tg or Tm), especially for heat-sensitive API. Carriers should also have a low hygroscopicity and be nontoxic.
- Selecting a polymer with inadequate thermoplastic characteristics can result in a non-uniform extrudate phase with potential crystallinity and degraded API.



# Drug Products Produced Using HME Have Complex Formulations (7)



## Inactive Ingredients: *Plasticizers*

- Plasticizers are typically low molecular weight compounds and are used to soften polymers (which are typically used as HME carriers) to make them more pliable.
- Plasticizers are often used with polymeric carriers in HME to improve the conditions during processing or to improve the physical or mechanical properties of the final product.
- Plasticizers must be appropriately selected and controlled during the HME process. If plasticizers are improperly selected, a lack of API release from extrudate, higher melting temperature requirements (which may lead to degradation), and inadequate viscous flow during extrusion may result.
- The most commonly used plasticizers include citrate esters, fatty acid esters, sebacate esters, phthalate esters, and glycol derivatives such as polyethylene glycol and propylene glycol.

## Drug Products Produced Using HME Have Complex Formulations (8)



### Inactive Ingredients: *Other Inactive Ingredients*

- Other inactive ingredients such as antioxidants and light absorbers are used to improve the stability of the polymers, which are prone to degradation at high temperatures.
- Some commonly used antioxidants include edetate disodium (EDTA), citric acid and chain-breaking antioxidants such as butylated hydroxyanisole, butylated hydroxytoluene and vitamin E.
- Other inactive ingredients include thermal lubricants such as glyceryl monostearate and silicon dioxide, which help move the mixture through the extruder.
- These ingredients must be properly selected, characterized and controlled in consideration of the desired characteristics of the resultant formulation in order to maintain product performance.

# Drug Products Produced Using HME Have Complex Formulations (9)



## Conclusion

- Extrudate must remain a stable and amorphous solid solution of API within a matrix throughout the shelf life of the final drug product in order to achieve proper performance.
- Extrudate should have a uniform distribution of API in the matrix and a controlled level of impurities.
- It is critical for the formulation components (API and inactive ingredients) to be thermally stable during the extrusion process and for the formulation to be physically stable afterwards.
- Selection and control of raw materials and ratios of ingredients (e.g., API to carrier polymer) influence several attributes of extrudate and, in turn, the final product.

Drug products produced using HME have complex formulations and present demonstrable difficulties for compounding

# Drug Products Produced Using HME Can Have a Complex Drug Delivery Mechanism



- Extrudate formulation determines the solubility and dissolution of the API from the matrix. The drug delivery mechanism should ensure that the API does not recrystallize *in situ*, thereby decreasing solubility.
- Depending on the design of the final dosage form, the type of extrudate matrix, and the amorphous state of the API, the drug delivery rate can be modulated and controlled.
- The extrudate can be employed within products that microencapsulate, target delivery, mask taste, film coat, modify release, and use nanotechnology.
- The qualitative and quantitative characteristics of API and inactive ingredient, physical design, and the site of action all influence the release rate and intended performance of drug products produced using HME.

## Drug Products Produced Using HME Can Have a Complex Drug Delivery Mechanism (2)



### Conclusion

- The mechanism by which API is released from the drug products produced using HME can be complex because it is dependent on a product design (e.g., immediate or sustained) that implicates API dissolution and solubility in an amorphous state within the extrudate to ensure appropriate drug delivery.
- This product design involves achieving and maintaining an amorphous state of the API in the extrudate, incorporation of the extrudate in the final dosage form, and selection of a carrier/API matrix that will release the drug at a predetermined rate.
- Precise control of raw materials, the extrusion process, and the final product are all necessary to ensure safety and efficacy.

The complexity of the drug delivery mechanisms of drug products produced using HME presents demonstrable difficulties for compounding

## Some Drug Products Produced Using HME are Complex Dosage Forms



- Some dosage forms of drug products produced using HME are complex because of the structural arrangement or distribution of the extrudate within the dosage form, the function or role of the extrudate in the dosage form's drug delivery mechanism, or the interaction of extrudate with other ingredients within the dosage form.
- For example, for topical drug products produced using HME, such as ointments, it is critical to appropriately process the extrudate in order to yield a particular viscosity, a drug release profile that enables either local or systemic drug delivery, and a texture (e.g., firmness) that is compatible for use in an ointment.
- In topical film drug products produced using HME, the extrudate needs to be produced in a way that provides for proper interaction with inactive ingredients so that the product adheres to the skin and delivers the API appropriately.

## Some Drug Products Produced Using HME are Complex Dosage Forms (2)



### Conclusion

- Extrudate can be incorporated into different dosage forms and for different routes of administration for a given therapy to increase bioavailability and product performance. In most dosage forms, the extrudate and other ingredients may need to be of a certain size and shape within the dosage form and arranged in a particular way to deliver the API properly.
- Drug products produced using HME require well designed controls of ingredient attributes and process parameters for predictable API release from a dosage form.
- Extensive product development and precise control over raw material selection and the production process are essential to evaluating the API release mechanism and profile, and other product performance characteristics.

The complexity of dosage forms produced using HME can present demonstrable difficulties for compounding

# Bioavailability is Difficult to Characterize and Control in Drug Products Produced Using HME



- FDA defines bioavailability as “the rate and extent to which the active ingredient...is absorbed from a drug product and becomes available at the site of drug action.” 21 C.F.R. § 314.3.
- Due to increased solubility of the API following extrusion, minor variations in the formulation of the extrudate can significantly impact bioavailability and, in turn, the safety and effectiveness of the product.
- Formulation and production processes for drug products produced using HME need to be well controlled to achieve a specified measure of API solubility and an optimal rate and extent of API absorption at the site of action.
- It is critical to measure the impact of recrystallization on bioavailability (*in vivo*) and utilize bio-relevant dissolution methods to predict performance (*in vitro*) to ensure that products have a consistent release rate of API that falls uniformly within predetermined and specific acceptable ranges.



# Bioavailability is Difficult to Characterize and Control in Drug Products Produced Using HME (2)

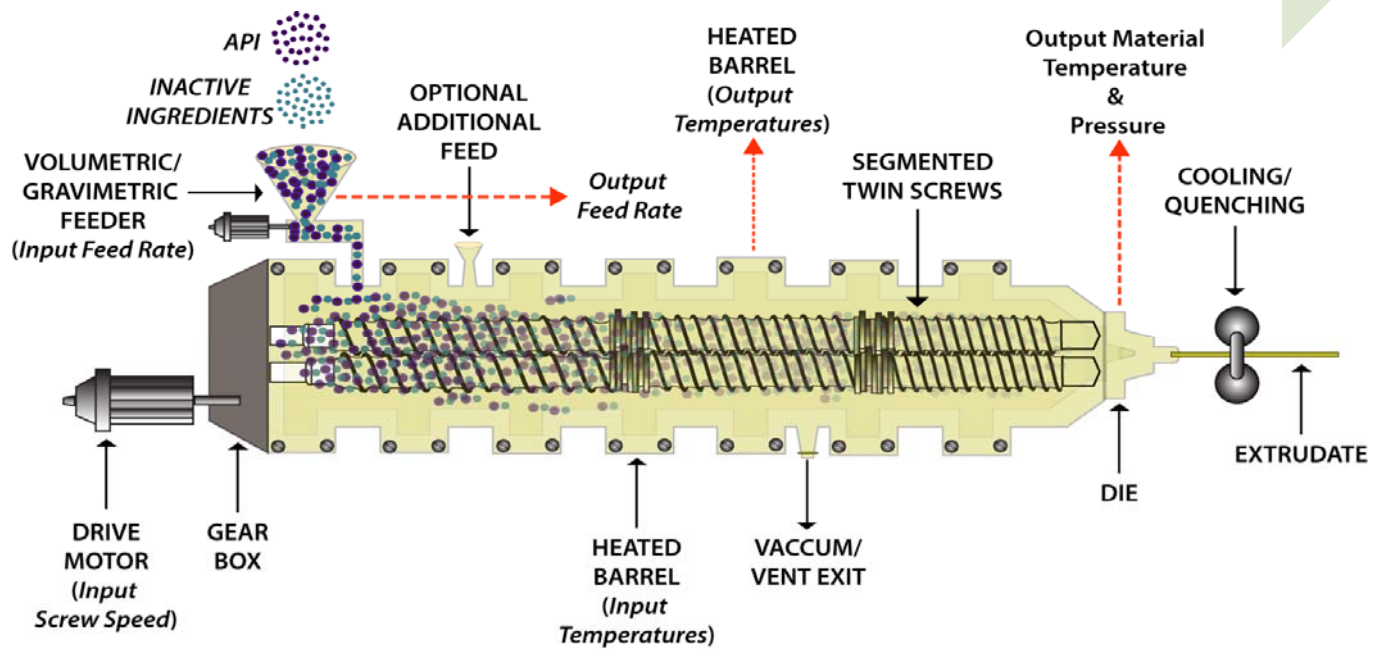
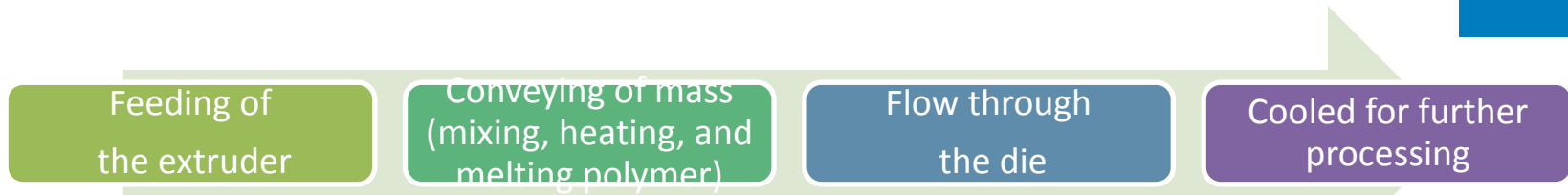


## Conclusion

- Characterizing and controlling the bioavailability of drug products produced using HME is complex.
- Subtle changes to any components or production processes could significantly impact a drug product's solubility and intrinsic dissolution, which may in turn influence local and systemic bioavailability.
- For drug products produced using HME, *in vitro* assessments, such as dissolution testing, alone are generally insufficient to accurately predict bioavailability and overall clinical effect. Rather, *in vivo* assessments are needed.

Characterizing and controlling bioavailability of products produced using HME is complex and presents a demonstrable difficulty for compounding

# HME Involves Complex Compounding Processes



# HME Involves Complex Compounding Processes (2)



## Process Controls

- Controls are necessary before, during, and after the HME process to ensure that the extrudate achieves and maintains critical quality attributes (amorphous state, uniformity, purity).
- A central electronic control unit used in HME processing controls the various process parameters such as screw speed, feed rate, temperatures along the barrel and the die, and the vacuum level for devolatilization.
- Extruders allow in-process monitoring and control of certain parameters, such as the temperature in the extruder, head, and die, as well as pressure in the extruder and die
  - Barrel temperature, feed rate, and screw speed are controlled parameters (i.e., having a set point) and motor load and melt pressure are monitored (measured responses) parameters.

# HME Involves Complex Compounding Processes (3)



## Screw Profile and Screw Speed

- The main assembly of the extruder consists of a drive motor and a gravimetric feeder. The drive motor controls the screw speed while the gravimetric feeder controls the feed rate.
- The screw speed and the feed rate are independent, predetermined, and specific, depending on the characteristics of the ingredients introduced into the extruder and the desired characteristics of the extrudate.
- Variations in the combination of screw speed and feed rate may affect the residence time of the mixture moving through the barrel, motor load, melt pressure, shear rates, and the temperature achieved by materials in the barrel.
- If these variations fall outside of the predetermined parameters, the extrudate may not exhibit the desired characteristics.

# HME Involves Complex Compounding Processes (4)



## Temperature

- Heat is generated in the extruder due to frictional heating within the barrel caused by the shearing of material between the rotating screws and between the screws and the wall of the barrel. The barrel is heated by heating elements that are mounted externally on the barrel.
- External cooling mechanisms are employed for adjusting and controlling the barrel temperature profile.
- Temperature controls are necessary to maintain the melt viscosity, which allows for proper conveying and mixing without thermally degrading the ingredients.
- Selecting the appropriate temperature profile along the barrel sections that will lead to robust conveying and melting without degradation of the extrudate can be difficult and important for extrudate quality.

# HME Involves Complex Compounding Processes (5)



## Cooling

- Once the extrudate exits the barrel through the orifice, it must be cooled at a predetermined and specified rate.
- The cooled extrudate is a glass (amorphous solid), which can be processed downstream using conventional pharmaceutical equipment for milling, cutting, blending, compressing, encapsulating, among others, depending on final dosage form.
- Variations in barrel temperature profiles, extrudate cooling rates and endpoints may alter the desired characteristics of the extrudate.

# HME Involves Complex Compounding Processes (6)



## Conclusion

- Specialized equipment under appropriate controls is critical for ensuring product quality.
- The extruder must be properly calibrated based on the characteristics of the ingredients fed into the extruder and the desired characteristics of the extrudate.
- Poor technique or control at any step will likely result in a product that does not achieve or maintain critical quality attributes.
- For example, uncontrolled processing can lead to unstable, non-uniform, and crystalline extrudate, which may result in diminished API bioavailability and in turn may adversely affect the safety and effectiveness of the drug product.

HME is a complex compounding process that presents demonstrable difficulties for compounding

# Drug Products Produced Using Hot Melt Extrusion Necessitate Complex Physicochemical or Analytical Testing



## Raw Materials Testing

- Rigorous characterization of the ingredients processed by HME is important to avoid a negative impact on the safety and effectiveness of HME drug products.
- Raw material properties, such as melt viscosity, thermal properties, and impurity content, can often impact the characteristics of the extrudate; raw material properties may vary from manufacturer to manufacturer, and across batches.
- FDA is not aware of available standard raw material testing methods (e.g., those found in the United States Pharmacopeia) that capture specific aspects of melting and crystallinity.
- Conducting complex methods of testing of raw materials used in HME is critical for ensuring processability of the components, the quality of the extrudate, and proper performance of the final drug product, and may require the use of specialized testing tools and equipment.



# Drug Products Produced Using Hot Melt Extrusion Necessitate Complex Physicochemical or Analytical Testing (2)



## Product Quality Testing

- A measurement system that properly characterizes the extrudate is complex because it incorporates multiple complementary methods to interpret similar properties.
- Properly determining the extrudate quality is not always possible through the interpretation of a single analytical technique and requires a complex analysis of supportive data.
- A critical quality attribute of the extrudate is an amorphous phase API in a carrier matrix
  - Analytical methods are needed to detect whether there is a single T<sub>g</sub> for the extrudate, confirming a single amorphous phase.

# Drug Products Produced Using Hot Melt Extrusion Necessitate Complex Physicochemical or Analytical Testing (3)



- Microscopy: for particle size and crystallinity, to detect the presence of drug crystals or air bubbles within the extrudate
- X-Ray Powder Diffraction (XRPD) and Spectroscopy: for detecting crystallinity and composition
- Non-sink dissolution: for drug release performance and stability
- Thermal analysis: differential scanning calorimetry (DSC) and modulated differential scanning calorimetry (mDSC) to qualitatively confirm that the extrudate has a single T<sub>g</sub>, identify a value for the T<sub>g</sub>, and verify the lack of a melting point corresponding to the drug substance as evidence of amorphous state; to analyze how the T<sub>g</sub> changes as a function of humidity; to rank-order formulations based on the value of the T<sub>g</sub> at a constant equilibrated humidity.

## Drug Products Produced Using Hot Melt Extrusion Necessitate Complex Physicochemical or Analytical Testing (4)



- Thermomechanical analyzer (TMA) and dynamic mechanical analysis (DMA) to measure Tg and for characterizing a product's viscoelastic property.
- Thermogravimetric analysis (TGA): to evaluate the solvent content and thermal degradation of the individual formulation components as well the final extrudate.
- High performance liquid chromatography (HPLC) to test purity and assay and to perform related substance test, in order to check for any chemical degradation of the drug substance under the HME processing conditions.

# Drug Products Produced Using Hot Melt Extrusion Necessitate Complex Physicochemical or Analytical Testing (5)



## Stability

- Ensuring the stability of a drug product produced using HME is a major challenge during production, storage, and administration.
- Typically, stability of the extrudate in the final product should be evaluated during the initial stages of product development. Recrystallization of API after extrusion should be directly measured.
- Typically, extrudate in the finished dosage form should be evaluated using a combination of accelerated, stressed, and long term stability tests to understand its behavior when exposed to humidity and temperature.
- Hygroscopicity of the extrudate can be significant, due to presence of polymer, which in turn reduces  $T_g$  and increases potential for recrystallization.
- Stability testing is critical for defining appropriate storage, handling, and packaging conditions.

# Drug Products Produced Using Hot Melt Extrusion Necessitate Complex Physicochemical or Analytical Testing (6)



## **In-Process Measurements for HME**

- Physicochemical characterization of the extrudate formed during HME is necessary to properly assess its properties and performance in the finished drug product.
- Novel analytical methods are often introduced as in-process controls for determining whether the extrudate is acceptable for continued processing.
- Process analytical technology (PAT) tools such as Near Infrared (NIR) and Raman spectroscopy can be employed to monitor and control the continuous HME processes.
- NIR can be used to monitor critical quality attributes such as content uniformity and moisture content, as well as extruder operation stability
- NIR or Raman can be used for assessing polymer layer thickness in multi-polymer systems.
- Raman can be employed to monitor the polymorphic form of the drug during the extrusion process.

# Drug Products Produced Using Hot Melt Extrusion Necessitate Complex Physicochemical or Analytical Testing (7)



## Conclusion

- Physicochemical and analytical testing performed before, during, and after the HME process to evaluate thermal properties, recrystallization, dissolution, and uniformity requires specialized analytical devices and procedures for accurate measurement.

Physicochemical and analytical testing required for production of drug products produced using HME is complex and presents demonstrable difficulties for compounding

# Risks And Benefits To Patients Of Compounded Drug Products Produced Using HME



- Drug products produced using HME can benefit patients due to enhanced bioavailability, controlled delivery rates, and stabilized formulations.
- Compounded drugs are not FDA-approved, but they can serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product.
- The Agency is not aware of any human drug compounders that produce drug products using HME.
- Such products could potentially benefit patients if they are produced with taste-masking properties suitable for children or are in dosage forms that are suitable for patients with swallowing difficulties, such as mini-tablets, and liquid suspensions.

# Risks And Benefits To Patients Of Compounded Drug Products Produced Using HME (2)



## Conclusion

- Compounding of drug products using HME would pose a significant risk to patients.
- HME process design complexities and the relationship between inactive ingredient and API of products produced through HME directly impacts bioavailability, release and performance. These in turn affect drug product effectiveness and safety.
- Substituting or removing inactive ingredients, such as polymers, plasticizers, or surfactants, would likely change the solubility and release characteristics of the product, and, in turn, may adversely impact product performance.
- Consistent quality controls for raw materials, the extrusion process, and final product, are all essential for predictable and reproducible API release, which directly affect the safety and effectiveness of the product.

Any potential benefit of compounded drug products produced using HME would be outweighed by the risks



## Recommendation



- We have evaluated the category of drug products produced using HME as a candidate for the Difficult to Compound List.
- Based on an analysis of the evaluation criteria, we believe that drug products produced using HME present demonstrable difficulties for compounding that reasonably demonstrate and are reasonably likely to lead to an adverse effect on the safety or effectiveness of such products.
- Taking into account the risks and benefits to patients, we believe that products produced using HME should be included in the Difficult to Compound List under sections 503A and 503B of the FD&C Act.

