COMPOUNDERS UNDER SECTION 503A OF THE FD&C ACT: QUALITY STANDARDS AND FDA FINDINGS

Pharmacy Compounding Advisory Committee Meeting
May 8, 2017

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Objectives

- To follow-up on questions from the last PCAC meeting, this presentation will describe:
  - Quality standards applicable to compounding under section 503A
  - Findings from FDA inspections

The manufacturing standards maintained impact the quality and safety of compounded drug products.
Compared to drugs compounded in outsourcing facilities, drugs compounded in section 503A compliant pharmacies are subject to less rigorous manufacturing standards and are potentially at greater risk of product quality problems, such as variability in potency and purity.
Compounding Under Section 503A

- Includes state-licensed pharmacies, federal facilities, and physician compounders
- Number in operation: thousands
- Facilities are not licensed or registered by FDA
  - States conduct day-to-day oversight and FDA conducts limited surveillance of these facilities
- All compounders are considered manufacturers under the FD&C Act
Inspections*

As of November 27, 2016, FDA has:

• Conducted more than 350 inspections, including 85 inspections of outsourcing facilities
• Issued more than 130 warning letters
• Issued more than 30 letters referring inspectional findings to state regulatory agencies
• Overseen about 100 recalls involving compounded drugs
• Worked with the Department of Justice on a number of civil and criminal enforcement actions

* Statistics include facilities that compound under sections 503A and 503B of the FD&C Act
Percent of Warning Letters Issued to Facilities Operating Under Section 503A Containing Certain Violations of the FD&C Act

Warning Letters issued between 12/6/13 and 12/8/16 (n= 96) and posted on www.fda.gov as of March 2, 2017
Form FDA 483

• Issued at the end of an inspection to an entity’s management when an investigator has observed conditions that *may* constitute violations of the FD&C Act

• Does not constitute a final Agency determination of whether any condition is in violation of the FD&C Act or any relevant regulations
This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.
Warning Letter

• Issued to an entity when FDA finds that the entity has significantly violated the law

• Identifies the violation and makes clear that the entity must correct the problem

• FDA may perform a follow-up inspection to ensure that the entity’s corrections are adequate
Section 503A Exemptions

• Under section 503A, drug products that are compounded according to certain conditions are exempt from:
  – Premarket approval requirements
  – Requirements for labeling with adequate directions for use
  – CGMP requirements

If a drug is not compounded in accordance with the conditions in section 503A, it does not qualify for the exemptions in that section and is subject to the approval, labeling with adequate directions for use, and CGMP requirements.
Examples of Section 503A Conditions

• Drug must be compounded by a licensed pharmacist in a state-licensed pharmacy or Federal facility, or by a licensed physician
• Patient-specific prescriptions
• Bulk drug substances must be:
  – USP/NF monograph OR FDA approved drug OR on “503A bulks list”
  – Manufactured by a firm registered under section 510
  – Accompanied by a valid certificate of analysis
• Difficult to compound list
• Copies restrictions
• Anticipatory compounding restrictions
• Withdrawn or removed list
503A: Current Inspection Procedure

• Effective August 1, 2016
  – Investigators make a preliminary assessment of whether an entity is compounding in accordance with conditions under 503A
  – Observations that represent deviations solely from FDA’s current CGMP requirements are not included on Form FDA 483 unless it appears based on that preliminary assessment that the entity does not qualify for the exemptions under section 503A
503A: Current Inspection Procedure

• Effective August 1, 2016 – continued
  – FDA reviews the evidence after the inspection to determine whether the entity is compounding in accordance with the conditions of section 503A

  – FDA intends to consider citing CGMP violations in any regulatory action it pursues when the Agency’s more thorough post-inspection review finds that the conditions in section 503A are not met
Insanitary Conditions and Other Requirements of the FD&C Act

• Although drug products compounded in accordance with the conditions of 503A are exempt from certain requirements of the FD&C Act, they remain subject to all other provisions in the Act, including the prohibition on insanitary conditions.

• FDA continues to include observations on Form FDA 483 that appear to constitute insanitary conditions or appear to violate other requirements of the FD&C Act without regard to the investigator’s preliminary assessment of a entity’s status under section 503A.
Insanitary Conditions

• Section 501(a)(2)(A) of the FD&C Act
  – A drug is deemed to be adulterated “if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health.”

• Draft guidance issued Aug. 3, 2016
  – *Insanitary Conditions at Compounding Facilities*
  • Comment period closed October 3, 2016
Insanitary Conditions

Applicable to:
- Sterile and/or non-sterile drugs
- Sterile drugs
  - Aseptic practices
  - Equipment and facilities
  - Sterilization
  - Cleaning and disinfecting
Inspections: Insanitary Conditions

- Use of non-sterile disinfectants in aseptic processing areas
- Poor personnel practices
  - Exposed skin and hair
  - Poor aseptic technique
  - Disruption of airflow while working in a laminar flow hood (LFH)
- Non-functioning HEPA filters and LFHs in aseptic processing areas
- Sterile drugs mixed with nonsterile components without further sterilization
Insanitary Condition Example

Visible microbial contamination on a ceiling tile in a clean room
Insanitary Condition Example

Filth under the hood including multiple pieces of medical supply waste and dust build up in the pre-filter for the ISO 5 hood
Insanitary Condition Example

The glove box that provides ISO 5 conditions where aseptic processing operations occur, was located in an unclassified carpeted room where the room air was not HEPA filtered. Note the wooden stool.
Insanitary Condition Example

Gowned employee working in the cleanroom, exposing legs
Insanitary Condition Example

The HEPA filter located immediately above the ISO 5 workbench was observed to have been stained on the filter surface.

The HEPA filter stain was due to drug product which had exploded due to excessive pressure applied when forcing non-sterile product through a sterilizing filter. The device used to force the product sterilizing filter was a stainless steel caulking gun that was not sterilized.
Insanitary Condition Example

Sleeve used in the aseptic glove box used for aseptic manipulations is damaged
Insanitary Condition Example

Toaster oven used to dry heat sterilize and depyrogenate glassware; oven was not capable of reaching high enough temperature to be effective
Insanitary Condition Example

Ceiling above the doorway to cleanroom with exposed insulation
Insanitary Condition Example

Kitchen dishwasher (supplied with tap water) and home detergent used to clean equipment and utensils that comes in contact with product intended to be sterile – no subsequent cleaning step
Insanitary Condition Example

Insects (vermin)
dead or alive
Serious Adverse Events and Product Quality Defects*

• Compounded multivitamin capsules containing a very high dose of vitamin D3 (cholecalciferol) leading to several adverse events potentially associated with the compounded capsules

• 15 patients developed bloodstream infections and 2 died after receiving contaminated compounded calcium gluconate injectable drug product
  – FDA identified insanitary conditions at the facility and confirmed bacterial contamination in the calcium gluconate

* Both events occurred at facilities operating under section 503A
Clean Room Example

Pellet production clean room
Clean Room Example
Equipment Example

Automated Compounding System
Equipment Examples

Incubators

Autoclave
Summary

• FDA’s oversight efforts have had a significant public health impact

• Compounders must meet all of the conditions under section 503A for their drugs to be exempt from CGMP requirements

• All drug manufacturers, including compounders, remain subject to the prohibition on insanitary conditions

• FDA continues to work to protect patients from poor quality drugs
Nicotinamide Adenine Dinucleotide (NAD)

Pharmacy Compounding Advisory Committee Meeting
May 8-9, 2017

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Nomination

• Nicotinamide adenine dinucleotide (NAD) has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for “reducing fatigue in multiple sclerosis” (MS)

• Nominated route of administration and dosage form: oral capsules
Physical and Chemical Characterization

- Molecular formula: $\text{C}_{21}\text{H}_{27}\text{N}_{7}\text{O}_{14}\text{P}_{2}$
- Well characterized structure
- Endogenous substance comprising two nucleotides
- Soluble in water
- Unstable - will degrade:
  - At temperatures above $-20^\circ\text{C}$
  - In alkaline pH
  - When exposed to light
  - When exposed to moisture
- NAD may degrade to byproducts such as nicotinamide mononucleotide and adenosine monophosphate, which may further degrade to several byproducts including nicotinamide riboside and nicotinamide
Physical and Chemical Characterization (2)

- **Synthetic route:** NAD is typically manufactured via yeast fermentation

- **Impurities:** Manufacturing components and degradation products of NAD

**Conclusion:**
- NAD is well characterized physically and chemically
- NAD will be unstable when compounded in the nominated oral capsule dosage form under ordinary storage conditions
- NAD stability issues call into question whether the formulations used in the various studies that are discussed in this presentation provided the dose of NAD that was reported
General Pharmacology

• NAD is synthesized de novo from tryptophan or recycled/salvaged from a number of substances (e.g., nicotinic acid, nicotinamide, nicotinamide riboside)

• NAD’s functional role in humans
  – Coenzyme for energy metabolism and production
  – Source of adenosine diphosphate (ADP)-ribose in enzymatic post-translational modifications of proteins

• Potential benefits of NAD supplementation from study in various proof-of-concept animal models
  – NAD may help to protect against teratogenicity, liver damage, DNA damage and infarct formation
Pharmacokinetics/Toxicokinetics

• Nonclinical
  – NAD may be absorbed in the small intestine of rodents
  – NAD is hydrolyzed to various compounds that are predominantly excreted in the urine
  – 21-day repeat dose study did not show NAD accumulation
  – When administered intravenously, NAD reached the brain in rodents
  – No toxicokinetic data were found

• Clinical
  – No pharmacokinetic data were found
Nonclinical Safety

• Acute toxicity:
  – LD$_{50}$ in mice is 4.3 g/kg body weight via intraperitoneal injection

• No studies were found for the following:
  – Repeat dose toxicity
  – Genotoxicity
  – Developmental and reproductive toxicity
  – Carcinogenicity
Adverse Event Reports

• Four published clinical trials (non-MS patients) with oral dosing; no safety data reported

• The voluntary reporting system cases contain insufficient information about the ingredients in the products consumed and/or the concomitant use of multiple substances
  – FDA Adverse Event Reporting System (FAERS)
  – CFSAN Adverse Event Reporting System (CAERS)
Safety of Related Compounds

• Some safety information may be derived from related compounds
  – NAD may degrade to nicotinamide riboside and nicotinamide
  – There are human data and dosing guidelines for administration of niacin, and for the purposes of these data and guidances, the term niacin encompasses both nicotinamide and nicotinic acid (Recommended Dietary Allowance: 15 mg niacin)
  – Doses ≥ 1000 mg of nicotinamide were associated with gastrointestinal adverse events, and doses ≥ 3000 mg were associated with signs of liver toxicity
  – The nominated dose of 5 mg NAD is comparable to daily dietary requirement of niacin

• Once a substance is included on the List of Bulk Drug Substances that can be used to compound under section 503A, the substance can be used to compound drug products for any use, and without limits on dosing
Safety Conclusion

• Insufficient nonclinical toxicity data for NAD to fully assess safety profile

• Minimal clinical safety data available for NAD
  – Data from related compounds may provide some assurance of safety for low milligram doses
Effectiveness

• No published studies were found that evaluated the effects of exogenous NAD administration in the treatment of MS-associated fatigue or MS

• One published study suggests that NAD levels are decreased in MS patients

• Multiple FDA-approved MS drugs
  – None has a specific indication for treatment of MS-associated fatigue, a common symptom of MS

Conclusion:

– Insufficient information exists to evaluate effectiveness of NAD for treatment of MS-associated fatigue or MS
Historical Use in Compounding

- Insufficient information available to determine how long NAD has been used in pharmacy compounding
- Topical and injectable compounded formulations of NAD are advertised on the internet by US pharmacies and clinics
- Extent of use cannot be determined
- NAD is not listed in the British, European, or Japanese Pharmacopeias
- NAD is currently marketed as a dietary ingredient in dietary supplement products
Recommendation

A balancing of the four evaluation criteria weighs against NAD being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)

Pharmacy Compounding Advisory Committee Meeting
May 8-9, 2017

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Nomination

• Nicotinamide adenine dinucleotide disodium reduced (NADH) has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for “use in the treatment of chronic fatigue syndrome” (CFS)
  – The term CFS will be used during this presentation to be consistent with the nomination

• Nominated route of administration and dosage form: oral capsules
Physical and Chemical Characterization

- Molecular Formula: $C_{21}H_{29}N_7O_{14}P_2$
- Well characterized structure
  - Endogenous substance comprising two nucleotides
  - Reduced form of NAD
- Soluble in water
- Unstable - will degrade:
  - At temperatures above -20°C
  - In acidic pH (e.g., stomach acid)
  - When exposed to oxygen, light or moisture
Physical and Chemical Characterization (2)

• **Synthetic route:** NAD is produced from yeast and reduced to form NADH

• **Impurities:** Manufacturing components and degradation products of NADH

**Conclusion:**
- NADH is well characterized physically and chemically
- NADH will be unstable when compounded in the nominated oral capsule dosage form under ordinary storage conditions and after ingestion, in stomach acid
- NADH stability issues call into question whether the formulations used in the various studies that are discussed in this presentation provided the doses of NADH that were reported
• NADH is involved in a wide range of biological reactions

• The ratio of

  \[ \text{NAD (oxidized form)} / \text{NADH (reduced form):} \]

  – Regulates the activity of various enzymes, including those involved in glycolysis, tricarboxylic acid (TCA) cycle and fatty acid oxidation

• The mechanism by which NADH might exert an effect, if any, in CFS is unknown
Pharmacokinetics

• Nonclinical
  – In vitro study suggests NADH may be absorbed in the small intestine
  – In vivo studies suggest:
    • Urinary excretion of nicotinamide metabolite is increased with intraperitoneal (IP) but not oral dosing
    • Bioavailability of NADH to the CNS may be IV > IP > Oral
  – No toxicokinetic data were found

• Clinical
  – No pharmacokinetic data were found
Nonclinical Acute Toxicity

• 14 day study in dogs
  – Oral dose (20, 100, and 150 mg/kg/day enteric coated tablet)
    • No overt signs of toxicological effects observed and no dose response
  – IV dose (up to 1000 mg/kg/day):
    • Dose related decrease in body weight, food consumption
    • Clinical signs at 500 mg/day included tremors, blood pressure and heart rate changes
    • Histology showed mononuclear, inflammatory perivascular infiltrate cuffing of blood vessels in the brain
Nonclinical Repeat Dose and Chronic Toxicity

• 26-week study in rats
  – Oral dose (5 mg/day of enteric coated tablet)
  – Potential ocular toxicity was observed in two female rats

• No studies were found for the following:
  – Genotoxicity
  – Developmental or reproductive toxicity
  – Carcinogenicity
Adverse Events: Voluntary Reporting

- FDA Adverse Event Reporting System (FAERS) - one case identified; confounded by use of multiple drug, dietary and herbal supplements
- CFSAN Adverse Event Reporting System (CAERS) - no cases identified
Adverse Events: Clinical Studies

• 2 trials in CFS (oral administration)
  – Several non-serious events reported

• 12 trials for other conditions (oral, IV, sublingual, or topical application)
  – Did not report safety information (5 trials), or
  – Patients experienced no adverse events (7 trials)
Safety Conclusion

• The nominated capsule strength of 5-20 mg NADH is comparable to the daily dietary requirement of niacin
• Niacin is associated with adverse events at higher doses
  – Once a substance is included on the List of Bulk Drug Substances that can be used to compound under section 503A, the substance can be used to compound drug products for any use, and without limits on dosing

Conclusion:
  – Insufficient nonclinical toxicity data for NADH to fully assess safety profile
  – Minimal clinical safety data available for NADH
    • Data from related compounds may provide some assurance of safety at low doses
Chronic Fatigue Syndrome

- CFS is a serious disease characterized by persistent fatigue accompanied by additional diverse symptoms

- The disease is known by various names such as myalgic encephalomyelitis
  - Various diagnostic criteria are utilized

- The etiology of CFS is unknown

- There are no FDA-approved treatments for CFS
Clinical Studies of NADH in CFS

• Forsyth et al. (1999)
  – Double blind, crossover study 10 mg enteric coated NADH tablet per day versus placebo
  – 4 week duration on each treatment, with 4 week washout between treatments
  – 50-item symptom questionnaire on various symptoms
  – 10% improvement was reported by 8/26 NADH and 2/26 placebo patients
Clinical Studies of NADH in CFS

• Santaella et al. (2004):
  – 12 months of treatment with 5-10 mg NADH per day versus nutritional and psychological therapy (n = 20)
  – Symptom scoring questionnaire completed at 0, 3, 6, 9 and 12 months
  – Decrease in severity of symptoms relative to baseline was observed in both groups, but no statistically significant differences between groups were identified at any time point

Effectiveness Conclusion
  – Clinical studies do not establish efficacy of NADH compared to placebo or other therapeutic measures
  – Stability of NADH in study formulations is unknown and may affect study outcomes
Historical Use in Compounding

• Insufficient information available to determine how long NADH has been used in pharmacy compounding

• Based on internet searches, NADH is and has been compounded in oral, topical, and injectable formulations
  – Extent of use cannot be determined

• NADH is not listed in the British, European, or Japanese Pharmacopeias

• NADH is currently available as a dietary ingredient in dietary supplement products
Recommendation

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

Pharmacy Compounding Advisory Committee
Meeting
May 8-9, 2017

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Nomination

• Nettle (*Urtica dioica* L.), referred to in this presentation as UD, has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for glycemic control

• No route of administration or formulation was proposed
Physical and Chemical Characterization

• UD is a herbaceous perennial flowering plant known as common nettle or stinging nettle

• Physicochemical profile is not well characterized
  – Complex mix of compounds
  – Total percentage of fully characterized and quantifiable compounds are low and can vary from batch to batch
  – Chemical profiles of the botanical raw material UD may vary significantly under different cultivation conditions and for various plant parts (e.g., leaf, stem, aerial parts, roots)
  – No specific method has been identified to assure quality control for UD’s use in compounded formulations
Major Nettle Components

Terpenoids (e.g., oleanolic acid)

Fatty acids (e.g., α-dimorphecolic acid)

Coumarins (e.g., scopoletin)

Ceramides

Lignans (e.g., neoolivil)

Other identified compounds

Homovanillyl alcohol

p-hydroxybenzaldehyde

Plus, phenylpropanes, polysaccharides, sterols, and lectins
Potential Impurities

• Various *Urtica dioica* subspecies, or other *Urtica* species such as *Urtica urens* L. (known commercially as dwarf nettle)

• Other botanicals (e.g., *Lamium album*, commonly known as white dead nettle)

• Heavy metal impurities found naturally in the soil, pesticide residue

• Manufacturing impurities:
  – Amino acids
  – Residual organic solvents
  – Heavy metal impurities
  – Bioburden
  – Inorganic impurities

**Conclusion:** *Urtica dioica* is not well characterized. Components may vary under various cultivation conditions and among plant parts.
General Pharmacology

- Limited pharmacologic data available for specific component(s) or formulation(s) of nettle
  - Variability in the plant materials
  - Differences in content of active components based on preparation (e.g., aqueous, oil, alcoholic, hydroalcoholic extracts)

- Many potential pharmacologic actions have been investigated for nettle:
  - Anti-oxidant, immunomodulator, anti-nociceptive, muscle relaxant, diuretic, anti-depressant, anticonvulsant, hypo/hyperglycemic agent, analgesic, blood pressure lowering agent

- Varied physiological responses in animal models of diabetes including decrease, increase, or no change in blood glucose levels
Pharmacokinetics

• Oral PK data from rats measured a single component of nettle root, 3,4-divanillyltetrahydrofuran (DVTF) (Shan et al. 2016)
  – Maximum plasma concentration reached within 2 hours
  – DVTF undetectable after 24 hours of dosing

• Oral dosing of nettle in mice was associated with a change in activity of several drug metabolizing enzymes (CYP P450) and antioxidant enzymes (Ozen and Korkmaz 2003)
  – Unknown whether these changes affect metabolism of nettle in animals or humans, or
  – Whether these changes impact the metabolism of other substances (e.g., concomitant drugs) that share the same metabolic pathways

• No other nonclinical pharmacokinetic/toxicokinetic data were found

• No clinical pharmacokinetic data were found
Nonclinical Safety

• Acute toxicity
  – Intraperitoneal, aqueous extract of UD in mice: LD$_{50}$ 3.5-3.625 g/kg: doses above 750 mg/kg were associated with decrease in spontaneous activity, loss of muscle tone, hypothermia
  – Oral, aqueous extract of UD in mice: LD$_{50}$ 1.7 g/kg
  – Oral/intraperitoneal, ethanolic extract of UD in rats and mice: LD$_{50}$ up to 2 g of dried herbal substance/kg
• Repeat dose toxicity
  – 14-day study in rats fed hexane UD extract by oral gavage
  – Minor clinical chemistry findings include:
    • Decrease in lymphocytes (800 mg/kg)
    • Increase in packed cell volume (≥400 mg/kg)
    • Increase in mean corpuscular hemoglobin (≥200 mg/kg)
    • Decrease in alkaline phosphatase (≥200 mg/kg)
  – No signs of major toxicity up to 800 mg/kg body weight (e.g., survival, behavior, histopathological findings)
  – No association between clinical chemistry changes and overall health profile of treated rats
Nonclinical Safety (3)

- Genotoxicity
  - A number of studies were conducted to assess the potential for nettle (herb, seed, oil) to cause genotoxicity
  - No conclusion could be drawn due to inadequate study design or incomplete data reporting

- Developmental and reproductive toxicity
  - A single study was identified in the literature (Sharma et al. 1983)
  - Decrease of implantation sites in pregnant rats exposed to nettle; study was not considered adequate
  - No data on embryofetal or pre/postnatal toxicity

- Carcinogenicity
  - No carcinogenicity studies were found in the literature
Adverse Event: Voluntary Reporting

• FDA Adverse Event Reporting System (FAERS)
  – 48 reports retrieved for UD
  – Causation cannot be established in any of these cases, due to concomitant medication or multi-ingredient products

• CFSAN Adverse Event Reporting System (CAERS)
  – 117 reports of adverse events in individuals using products containing nettle
  – 113 of these involved use of products containing multiple herbal ingredients
  – 4 of these reported UD as primary active ingredient ingested, but cases were attributed to inactive ingredients (n=2), burning sensation due to capsule chewing (n=1), and myocardial infarction deemed unrelated to UD ingestion by reporting physician (n=1)
Adverse Events: Recall & Case Reports

• Recalls related to product safety
  – 4 lots of nettle capsules were recalled by a major commercial supplier of US herbal dietary supplements due to excessive amounts of lead (Upton 2013):
    – Lots were traced to a single batch of raw material
    – No adverse events were reported in the publication

• Adverse events described in case reports (n= 4) include:
  – Diffuse edematous gingivostomatitis with positive allergy test, unilateral gynecomastia, galactorrhea, urticarial rash
Adverse Events: Clinical Trials

• Adverse event data were not reported in any of the publications (n=7) assessing nettle for the treatment of diabetes

• Adverse events from clinical trials in which UD was studied for the treatment of diseases other than diabetes: review articles (Chrubasik et al. 2007a; 2007b)
  – 10 clinical studies where aerial UD oral formulations were used to treat peripheral edema, arthritis (osteoarthritis and rheumatoid arthritis), and allergic rhinitis; adverse events included mostly mild gastrointestinal or allergic skin reactions
  – 34 clinical studies where “nettle root” was used to treat benign prostatic hypertrophy; most common adverse events were impotence and decreased libido
Safety Summary

• Insufficient nonclinical toxicology and pharmacokinetic data were found

• Limited systematically collected safety information regarding UD, despite large number of patients observed in clinical studies

• Available information based on formulations of UD with an uncharacterized composition

• Safety profile of UD is not adequately established
Clinical Studies in Type 2 Diabetics

- 7 publications reported outcomes associated with glycemic control
- 3 of the 7 publications appear to be derived from same study, with different set of endpoints reported in each publication (Namazi et al. 2011a; 2011b; 2012)
  - Randomized, blinded study of type 2 diabetic patients
  - Patients received either UD formulation of 100 mg/kg/day, divided (n=24) or identically colored placebo (water and ethanol mix) (n=21) in glass of water after each of three main meals for 8 weeks
  - Extracts of UD aerial parts were prepared with 60% ethanol, and were associated with levels of 45% ethanol in the final extraction solutions
  - Patients continued pre-study oral antidiabetic medication regimen
  - Possible treatment-related decrease in fasting blood glucose and percent HbA1c at end of study compared to controls, but details of statistical analysis are unclear
Clinical Studies in Type 2 Diabetics (2)

• 2 publications were from studies that were apparently related (Kianbakht et al. 2012; 2013)
  – Blinded, randomized, placebo-controlled studies in type 2 diabetic patients
  – Pre-study antidiabetic medication was continued, with addition of UD, for 12 weeks
  – The minor improvements in fasting glucose and HbA1c reported can not be relied on because of apparent errors in data reporting (duplicated data)
  – UD components from same extraction procedure performed on different occasions were assayed and found to be substantially different; potentially indicative of variable dosing
Clinical Studies in Type 2 Diabetics (3)

- Double-blind, randomized, placebo-controlled study in type 2 diabetic patients (Khajeh-Mehrizi et al. 2014)
  - 8 weeks of UD “extract” 100 mg/kg/day (n=24) or placebo (n=25)
  - Divided doses after each of three daily meals
  - No statistical difference noted between treated and placebo groups in mean fasting blood glucose
Clinical Studies in Type 2 Diabetics (4)

- Unblinded, parallel group study with 4 groups of men (Dabagh and Nikbakht 2016):
  1. Aerobic exercise alone (n=10)
  2. 10 g of UD leaves dried and ground to a powder (no extract) and mixed in yogurt for daily administration before breakfast (n=10)
  3. Combination of aerobic exercise and daily UD powder administration (n=10)
  4. Placebo (yogurt alone; n=10)

- Mean fasting blood sugar decrease was statistically greater for all active treatments compared to placebo

- Mean fasting blood sugar change of combination of UD and exercise was statistically significantly greater than for UD alone
Effectiveness Summary

- Published studies provide some suggestion that UD may affect glycemic control, but they do not provide substantive evidence of UD’s effectiveness.
- All available studies lack information regarding composition of the UD formulation.
- There are many FDA-approved products for the treatment of diabetes.
Historical Use in Compounding

- Nettle has been used as a medicinal agent since ancient times
- According to the literature, nettle has been used in pharmacy compounding for at least 7 years
- Based on internet searches, nettle leaf currently appears to be compounded in combination with other ingredients as a capsule
- Extent of use cannot be determined
- Nettle leaf, nettle root, and UD as the whole plant are listed in the European and British Pharmacopoeias
- Nettle is available as a dietary ingredient in dietary supplement products
A balancing of the four evaluation criteria weighs **against** nettle (*Urtica dioica*) being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.
Ubiquinol

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Elizabeth Marek, PharmD, Consumer Safety Officer, OUDLC, OC
Nomination

• Ubiquinol, 30% powder, has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for use as adjunctive therapy in glycemic control.

• Nominated route of administration and dosage form: oral capsules.

• Studies of CoQ10 were considered for ubiquinol evaluation; however, the eligibility of CoQ10 for use in compounded drug products is not being considered at this time.
Physical and Chemical Characterization

- Molecular Formula: $C_{59}H_{92}O_4$
- Minimally soluble in water
- Well characterized structure
- Unlikely to be stable under ordinary storage conditions
  - May be stable if formulated with antioxidants
- Reduced form of coenzyme Q10
Possible synthetic route: Ubiquinol is usually prepared from the reduction of ubiquinone (coenzyme Q10), which can be obtained from yeast fermentation.

Conclusion:

- Ubiquinol is well characterized as reduced form of CoQ10
- May be stable with the addition of antioxidants
General Pharmacology

• Ubiquinol and CoQ10 are endogenously synthesized and ingested from meats and produce

• Ubiquinol is:
  – An antioxidant in cells, protecting cell membranes and serum LDL from lipid peroxidation
  – Key in mitochondrial energy, ATP production

• In humans and most other mammals, CoQ10 is the most common coenzyme in this functional series
  – In rodents, CoQ9 is the most common form
  – There are numerous other coenzymes in the series serving similar functions in other living systems
Animal Model of Glycemic Control

- Study of streptozotocin (STZ)-induced diabetes in a rat model (Prangthip et al. 2016)
  - Ubiquinol treated rats were associated with a greater decrease in blood glucose levels than placebo at week 2 but the difference between ubiquinol and placebo treatments was not observed through weeks 3 and 4.
  - CoQ10 treated rats were associated with a greater decrease in blood glucose levels than placebo at weeks 2, 3 and 4.
  - Relevance of findings is unknown given predominance of CoQ9, rather than CoQ10, in rodents.
Pharmacokinetics

• Nonclinical
  – Bioavailable through 13 week dosing study in dogs

• Clinical
  – 3 single dose and 2 multiple dose pharmacokinetic studies
  – Readily absorbed following oral ingestion
  – Tmax of approximately 6 hours
  – Dose dependent increases in Cmax and AUC
  – Steady state achieved after 2 weeks; accumulation in plasma is unlikely based on decline in levels following discontinuation of dosing
Nonclinical Safety

• Acute toxicity
  – No adverse effects in male or female rats (n = 5/sex) following a single 5 g/kg dose (Hosoe et al. 2007)

• Repeat dose toxicity (Kitano et al. 2008)
  – 13 week oral gavage study in M/F rats (n = 5/sex) with doses up to 1200 mg/kg/day showed multiple signs of hepatic toxicity starting at 200 mg/kg/day; findings were pronounced among treated females
  – 13 week oral gavage study in female rats (n = 10/dose level) with doses up to 300 mg/kg/day did not produce hepatic toxicity
  – 13 week oral gavage study in dogs (n=3/sex/dose level) up to 600 mg/kg/day showed no clinical, laboratory or histopathological changes except decreased heart rate after dosing
Nonclinical Safety (2)

• Genotoxicity
  – Standard panel of genotoxicity assays did not show genetic toxicity activity
  – Battery included: bacterial reverse mutation, in vivo micronucleus test, chromosomal aberration assays

• Developmental and reproductive toxicity - no studies

• Carcinogenicity - no studies
Adverse Events: Voluntary Reporting

• FDA Adverse Event Reporting System (FAERS)
  – 39 cases in which serious events were reported
  – Insufficient information to establish whether ubiquinol was associated with reported drug-drug interactions, increased hepatic enzymes, or abnormal blood glucose levels in diabetic patients

• CFSAN Adverse Event Reporting System (CAERS)
  – 112 cases identified; use of other dietary supplements was not reported in 3 cases
  – In 2 cases, a patient experienced difficulty breathing several days after initiating ubiquinol; symptoms resolved within days after discontinuing ubiquinol

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Adverse Events: Clinical Studies

• 23 clinical studies of ubiquinol
  – Oral dosing up to 1200 mg per day
  – Safety data were not reported for 11 studies, including the only study of patients with type 2 diabetes

• There were 4 deaths among ubiquinol-treated sepsis patients
  – Independent safety review board ruled deaths unrelated to ubiquinol use (Donnino et al. 2015)
Various adverse events were reported in studies of healthy volunteers, autism patients, Chronic Fatigue Syndrome (CFS) patients, and recipients ≥ 60 years of age.

3 potentially serious adverse events reported:
- Enterocolitis (condition determined to have existed prior to trial) in one volunteer
- Deconditioning in one CFS patient
- Worsening asthma in one autistic child
Safety Conclusion

• Overall, existing nonclinical data are insufficient to determine safety for treatment of chronic disease such as diabetes

• Clinical safety profile has scant information and relationship between adverse events and ubiquinol is unclear
Ubiquinol Efficacy Studies

• 4-week pharmacokinetic study in healthy volunteers showed no clinically significant changes in glucose, HbA1c or insulin as safety parameters (Hosoe et al. 2007)

• Open-label, uncontrolled pilot study (Mezawa et al. 2012)
  – 9 type 2 diabetics used 200 mg ubiquinol daily for 12 weeks
  – 7 of 9 patients used concomitant antidiabetic drugs
  – HbA1c reduced from 8.7 to 8.2 mmol/L in ubiquinol group
  – No diabetic patient control group
  – Intra-group statistical comparisons only
  – Overall, inadequate design to assess ubiquinol as primary or adjunctive treatment
Coenzyme Q10 Efficacy Studies

• 7 clinical studies in type 2 diabetics
  – HbA1c and/or fasting plasma glucose improved in 2 studies, but study designs were insufficiently described to conclude clinical effect was due to CoQ10
  – In 5 studies, CoQ10 failed to show improvement in treated diabetic patients compared to placebo untreated diabetic patients

• 2 clinical studies in type 1 diabetics
  – No improvement in HbA1c or fasting blood glucose

• The applicability of these studies to ubiquinol is not well understood
Effectiveness Conclusion

• Insufficient data to support the use of ubiquinol as a primary treatment or adjunctive treatment.

• Many FDA approved treatments are available for use in glycemic control for use as sole treatments or as part of combination therapies.
Historical Use in Compounding

• Insufficient information available to determine duration of ubiquinol use in pharmacy compounding
• Based on a single retrospective claims study, it appears that ubiquinol has been used as an ingredient in compounded medications
• Extent of use cannot be determined
• Ubiquinol is not listed in the British, European, or Japanese Pharmacopeias
• Currently available as a dietary ingredient in dietary supplement products
Recommendation

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

Pharmacy Compounding Advisory Committee Meeting
May 8-9, 2017

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Nomination

• Vanadyl sulfate has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for use in the treatment of diabetes, hyperlipidemia and heart disease, and to prevent cancer

• Nominated route of administration: “slow intravenous” injection
Physical and Chemical Characterization

- Molecular formula: VOSO$_4$
- Highly soluble in water
- Stable under ordinary storage conditions as injectable solution
- Well characterized structure
Vanadyl sulfate can be synthesized from the reduction of vanadium pentoxide as follows:

\[ V_2O_5 + SO_2 + H_2SO_4 + 7 H_2O \rightarrow 2 \left[ V(O)(H_2O)_4 \right] SO_4 \]

No biological or functional role for vanadium has been identified in humans.

**Conclusion:** Vanadyl sulfate is an inorganic vanadium salt which is stable under ordinary storage conditions as an injectable solution.
Vanadium (V) is a naturally occurring element; it is one of 38 elements called transition metals.

Vanadyl sulfate can be found in drinking water and foods (meats, vegetables, fruits).

It exists in oxidation states ranging from -1 to +5, with the most common valence states of +3, +4, and +5.

Vanadyl sulfate (VS, VOSO₄), contains the most stable oxidation state, the tetravalent form (VO²⁺, vanadyl) of vanadium.

The tetravalent form is the most common intracellular form available, whereas the pentavalent form (VO³⁻) is most common in extracellular body fluids.
Background (2)

- The tolerable upper intake level (UL) of vanadium established by the Institute of Medicine (IOM), based on its safety evaluation, is 1.8 mg/day of elemental vanadium for adults
  - IOM has not identified a functional role for vanadium

- The Environmental Protection Agency has set a reference dose limit for chronic oral exposure to vanadium pentoxide in drinking water at 0.009 mg/kg/day
  - Listed on the EPA’s Drinking Water Contaminant Priority list due to insufficient information to support a regulatory determination of its safety

- Vanadium (+4, +5) is being studied by the National Toxicology Program (NTP)
  - Oral toxicity studies (carcinogenicity, reproductive toxicity) to evaluate safety of exposure to vanadium in drinking water and dietary supplements
Nonclinical Pharmacokinetics

• Vanadyl sulfate is absorbed by the gastrointestinal tract and transported in blood by albumin or transferrin to various organs and tissues

• Absolute bioavailability is approximately 16%; higher than other vanadium salts

• Studies of radiolabeled vanadium distribution following a single oral or intraperitoneal dose of vanadium sulfate:
  – Uptake peaks at 2–6 h after dosing
  – Highest uptake in bones, liver and kidneys with slow decline in levels after dosing

• Absorbed vanadium is excreted in the urine and unabsorbed vanadium is excreted via the feces
Nonclinical Toxicokinetics

• Vanadium can pass through the placental barrier of pregnant mice and is detectable in fetal tissues
• When vanadium dust is inhaled, it can accumulate in the lungs of both animals and humans
• No toxicokinetic studies for vanadyl sulfate were found in the literature
Clinical Pharmacokinetics

• Intravenous single dose of vanadate (+5 oxidation state) received by healthy volunteers (n=5) as an impurity of an albumin solution showed the following vanadium PK data (Heinemann et al. 2003):
  – 3-phase elimination with initial half lives of 1.2 and 26 hours, followed by a long terminal half-life of 10 days
  – The terminal elimination accounted for 80% of the AUC
  – The volume of distribution at steady state was 54 L
  – Excretion was mainly via the urine (52% of dose recovered in urine after 12 days); very small amounts still measureable in blood after 31 days
Nonclinical Safety: General

• Nonclinical studies show that the toxicity of vanadium compounds increases with higher vanadium valences — Pentavalent compounds appear to be the most toxic form of vanadium

• Toxicity of vanadium compounds is reported to be, in general, low via oral ingestion, moderate via inhalation, and high via injection

• All available nonclinical toxicology data for vanadyl sulfate are from studies of oral administration — No nonclinical toxicology data were available for vanadyl sulfate administered via the intravenous route
Nonclinical Acute Toxicity

• Exposure to single doses of various vanadium compounds in acute toxicity studies (oral and intraperitoneal) is associated with a wide range of toxicities including mortality, neurotoxicity, cardiotoxicity, respiratory, and hematological findings.

• Higher level of toxicity seen via the intraperitoneal injection compared to the oral route of administration (oral gavage, drinking water).
Nonclinical Repeat Dose Toxicity

• 4 week oral (gavage) toxicity study in streptozotocin (STZ)-induced diabetic and control rats
  – Vanadyl sulfate and 2 other vanadium salts were studied
  – Drug accumulation in kidneys, bones, spleen, liver, testes
  – Adverse effects included dose-related diarrhea, significant reduction in blood glucose and lipid levels

• 1 year oral toxicity study in STZ-induced diabetic and control rats
  – Increases in several organ weights
  – Increased incidence of glomerular and tubular degeneration; interstitial cell infiltration and fibrosis in kidneys; mucosal petechiae in stomach; Leydig cell tumors in non-diabetic, treated animals
  – Accumulation of vanadyl sulfate in kidneys, bones, liver, spleen and testes observed after 16 weeks of drug free recovery period, when vanadyl sulfate was no longer detectable in the plasma
Other Nonclinical Toxicity

• Genotoxicity
  – Several in vitro, ex vivo and in vivo assays (mice) were reported
  – Vanadyl sulfate can cause cytogenetic damage and has a clastogenic potential in both in vitro and in vivo assays

• Developmental and reproductive toxicity
  – Toxicities reported for vanadyl sulfate include adverse effects on male fertility in rats, embryofetal toxicity in mice, and prenatal and postnatal developmental toxicity in rats
  – Vanadyl sulfate can accumulate in the developing fetus as well as in the placenta, potentially causing fetal toxicities
Carcinogenicity

• Carcinogenicity studies conducted for vanadyl sulfate in mice by oral administration
  – In a drinking water study, vanadyl sulfate (5 ppm) did not increase the overall number of detected tumors
  – The incidence of malignant tumors in the vanadyl sulfate-treated mice was higher (60%) than in the concurrent control group (27%)
  – In a subsequent study in mice using a similar dose, a significant increase in tumor incidence was seen in vanadyl sulfate-treated females but not in males

• Clarification of these equivocal data is the stimulus for ongoing NTP studies (oral carcinogenicity study and a 2-generation study) to make an assessment regarding human safety
Adverse Events: Voluntary Reporting

• FDA Adverse Event Reporting System (FAERS)
  – One report of a patient with Crohn’s disease who experienced dehydration, vomiting, diarrhea with bleeding, and abdominal pain after taking vanadyl sulfate for an unspecified period of time; patient recovered after being hospitalized for 10 days

• CFSAN Adverse Event Reporting System (CAERS)
  – 1,341 reports; these cases contain insufficient information about the ingredients in the products consumed and/or the concomitant use of multiple substances
Adverse Events: Clinical Studies

• No safety literature was found on the administration of intravenous vanadium containing compounds

• Trials in diabetics with oral vanadyl sulfate 50 mg to 300 mg per day
  – Usually of short duration; common adverse events were gastrointestinal including nausea, vomiting, diarrhea and bloating

• Development program of bis(ethylmaltolato)-oxovanadium (IV) was halted because of nonclinical renal toxicity findings attributed to vanadium
Safety Conclusion

• Nonclinical
  – No data on the toxicity profile of vanadyl sulfate via the nominated route of exposure (injection)
  – Available studies suggest that vanadyl sulfate is associated with gastrointestinal and renal toxicities, accumulates in several organs, is genotoxic, and is a reproductive toxicant
  – Carcinogenicity studies with vanadyl sulfate showed equivocal results. Ongoing NTP studies addressing safety concerns

• Clinical
  – No safety data for intravenous administration
  – Oral administration up to 300 mg per day associated with gastrointestinal adverse effects
Efficacy in Diabetes/Hypoglycemia

• Five clinical studies in Type 2 diabetics
  – Small number of patients and limited duration
  – Lacked analytical comparisons between active treatment and placebo patients
  – Potential effect was not substantially demonstrated

• Study in Type 1 diabetics
  – Decrease in fasting blood sugar and insulin use over 30 months of treatment
  – No comparison between active and placebo treatments

• Study in patients with impaired insulin sensitivity – no change after 30 days of treatment
Efficacy: Other Conditions

• Hyperlipidemia
  – Type 1 diabetics treated for 30 months showed a decrease in total mean cholesterol (Soveid et al. 2013)
  – Patients with impaired glucose tolerance treated for 30 days showed an increase in triglycerides compared to placebo (Jacques-Camarena et al. 2008)
  – Suggestion of potential effect but insubstantial clinical study information

• Heart disease - No clinical studies of vanadyl sulfate or other vanadium compounds were found

• Prevention of cancer - No clinical studies of vanadyl sulfate or other vanadium compounds were found

• There are numerous FDA-approved drug products for the treatment of diabetes, hyperlipidemia, heart disease, and various types of cancer
Effectiveness Conclusion

- Vanadyl sulfate has been studied to a very limited extent in Type 1 diabetes, Type 2 diabetes, and impaired insulin sensitivity. Although there may be a potential treatment effect, vanadyl sulfate has not been adequately studied in the clinical setting.

- Changes in lipid status observed in diabetes trials suggest a treatment effect but are inadequate to support effectiveness.

- No trials for heart disease or prevention of cancer were found.
Historical Use in Compounding

- Compounds containing vanadium were used as early as the 19th century.
- Vanadyl sulfate has been used for years in pharmacy compounding as a capsule.
- One US pharmacy advertises use of “vanadium” as a component of an injectable compounded product.
- Extent of use cannot be determined.
- Vanadyl sulfate is not listed in the British, European, or Japanese Pharmacopeias.
- Vanadyl sulfate available as a dietary ingredient in dietary supplement products, all of which are taken orally.
Recommendation

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

Pharmacy Compounding Advisory Committee Meeting
May 8-9, 2017

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Nomination

• Artemisinin has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for use in the treatment of:
  – Malaria
  – Helminthic infections
  – Protozoal (toxoplasmosis) infections
  – Stomach ulcers
  – Cancer

• Nominated routes of administration: oral, injection (oral capsules 50-500mg; injections up to 240 mg)
Physical and Chemical Characterization of Artemisinin

- **Molecular formula:** $C_{15}H_{22}O_5$

- **Solubility:** Insoluble in water; usually extracted with hexanes, petroleum ether, or other organic solvents

- **Stability:** Stable under ordinary storage conditions

- **Structure characterization:** Well characterized

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Physical and Chemical Characterization of Artemisinin (2)

• **Possible synthetic route:** Artemisinin can be extracted and isolated from *Artemisia annua*

• **Likely Impurities:** Residual solvents, trace amount of degradation product of artemisinin

**Conclusion:** Artemisinin is an organic molecule; it is likely to be stable under ordinary storage conditions
Artemisinin: Scope of Review

• Artemisinin and its semi-synthetic derivatives are a family of sesquiterpene trioxane lactone agents that have been investigated largely for their anti-malarial activity.

• Artemisinin is the nominated substance. This discussion will include information on some of the derivatives because the mode of action is similar among all of the substances and there is insufficient information on artemisinin.
Structure of Artemisinin & Common Derivatives

Highly reactive endoperoxide bridge common among all structures
Mechanism of Action

- Exact mechanism of action for artemisinin and its derivatives is unknown
  - Highly reactive endoperoxide bridge of artemisinin and its derivatives generate reactive oxygen species and carbon-centered radical molecules that bind and modify proteins and DNA of parasites (including *Plasmodium*, *Toxoplasma*, and *Schistosoma*)
  - Endoperoxide bridge is critical for the inhibitory effects of artemisinin and its derivatives
Nonclinical Pharmacokinetics

• Artemisinin is rapidly absorbed (Tmax = 1hr in rats after oral administration)
• Highest concentrations found in liver, brain, plasma and lung
• Metabolized via the cytochrome P450 enzymes
• Largely eliminated via the urine (within 24 hrs after dosing in rats)
Toxicokinetics

• A single oral dose of artemisinin or repeated daily dosing of artemisinin for 5 days in male rats
  – Artemisinin is rapidly absorbed with a short plasma half-life following a single dose or repeated dosing.
  – Systemic exposure decreased significantly with repeated dosing (likely due to auto-induction) caused by first pass metabolism
Nonclinical Acute Toxicity

• Lethal dose for 50% of animals (LD$_{50}$) via intramuscular injection
  – 3840 mg/kg in mice, 2571 mg/kg in rats
  – Signs preceding death included behavioral changes, respiratory difficulties, and cardiac arrest

• A single intramuscular dose of artemisinin in dogs (0, 400 or 800 mg/kg) showed:
  – Neurobehavioral effects (dose related tonic and clonic convulsions, hyperactivity and vocalization)
  – Hematological findings (dose-dependent decrease in reticulocyte count)
Nonclinical Repeat Dose Toxicity

• 5, 7, 14-day studies in dog and rat showed no changes

• 14-day study in monkeys showed death at the highest dose (3 out of 4 animals died at 192 mg/kg/day)
  – Nonlethal dose findings included reduced appetite, decreased activity, decreased heart rate, and hematopoietic inhibition in bone marrow
Nonclinical Neurotoxicity Studies

- Nonclinical general toxicity studies and targeted neurotoxicity studies tested
  - Species included mice, rats, dogs, and monkeys
- Toxicity findings were related to dose level and duration
- Behavioral changes included tremor, restlessness, lethargy, abnormalities in balance and coordination (gait disturbance, jerking limb movements)
- Changes in auditory discrimination task tests, loss of spinal reflex, pain response reflex, and loss of brainstem and eye reflexes
- Histological examinations revealed extensive damage in brainstem nuclei of the reticular formation, the vestibular system, and the auditory system
Genotoxicity

• Artemisinin was negative for genotoxic activity
  – In vitro bacterial reverse mutation assay – up to 300 µg/plate
  – In vivo micronucleus test (mouse) – up to 846 mg/kg

• Artesunate was positive in several genotoxicity tests
  (e.g., COMET, micronucleus assays)
Other Nonclinical Safety

• Developmental and reproductive toxicity
  – Embryolethality, late resorptions, malformations (external, visceral, skeletal) in rodents, rabbits and monkeys
  – Highest sensitivity during mid to late stages of development
  – Adverse effects noted for spermatogenesis

• Carcinogenicity
  – No carcinogenicity studies were found for artemisinin or its derivatives
Nonclinical Safety Summary

- Significant treatment-related toxicities include mortality, neurotoxicity, hematotoxicity, embryolethality, and developmental toxicity
  - Dose-response relationship
  - Class effects for artemisinin and its derivatives

- Toxicities related to dose, treatment frequency, duration, administration route, physicochemical properties, and formulation
  - Developmental toxicities seen at doses relevant to human therapeutic doses
Human Pharmacokinetics

• Absorption
  – Artemisinin is rapidly absorbed with a short elimination half-life
  – Systemic exposure to artemisinin decreases with repeated dosing, likely due to auto-induction of drug metabolism

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1</th>
<th>Day 5</th>
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</thead>
<tbody>
<tr>
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<td>2780 (1742, 3817)</td>
<td>686 (112, 1260)</td>
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<tr>
<td>C max (ng/ml)</td>
<td>706 (477, 935)</td>
<td>134 (59, 210)</td>
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<td>Cl (L/hr)</td>
<td>299 (1.6, 2.3)</td>
<td>1618 (820, 2416)</td>
</tr>
<tr>
<td>T 1/2 (hr)</td>
<td>2.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

• Bioavailability
  – Oral bioavailability of aqueous formulation was lower (32%) than intramuscular oil suspension injection (IM > oral)
  – Intramuscular formulations may have greater inter-subject variability than oral formulations

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Human Metabolism

- Artemisinin is mostly metabolized by cytochrome CYP2B6, CYP3A4 and to a minor extent by CYP2A6
- Artemisinin induces CYP3A, CYP2B6, CYP2C19, and reduces activity of CYP1A2 and CYP2D6 (Likely to have drug-drug interactions with drugs metabolized through the cytochrome P450 pathways)
- None of the metabolites of artemisinin has the endoperoxide bridge (i.e., are inactive)
- Artesunate, artemether and arteether are metabolized by various cytochromes to dihydroartemisinin (active metabolite)

Graph is used with permission from PharmGKB: Source https://www.pharmgkb.org/pathway/PA165378192#PGG; M. Whirl-Carrillo, E.M. McDonagh, J. M. Hebert, L. Gong, K. Sangkuhl, C.F. Thorn, R.B. Altman and T.E. Klein.
Adverse Events: FAERS Data

- FDA Adverse Event Reporting System (FAERS) data associated with artemisinin use include 2 cases of hepatic dysfunction that may have been associated with use of artemisinin:
  - A 60 year old male patient took artemisinin for malaria prophylaxis; concomitant echinacea use. Jaundice was reported 5 days after last dose of artemisinin; liver biopsy showed drug-induced hepatitis
  - A 69 year old patient with breast cancer treated with anastrozole, artemisinin and radiation had elevated liver enzymes (ALT-700 U/L, AST – 400 U/L). Anastrozole and artemisinin use were discontinued; liver function tests (LFTs) returned to normal. Anastrozole restarted, unclear if artemisinin re-started. Eight weeks later, LFTs were normal

- Causality in both cases is suggestive of artemisinin-induced liver dysfunction, but confounded by concomitant medications/therapies and illnesses
Adverse Events: CAERS Data

- CFSAN Adverse Event Reporting System (CAERS) data associated with artemisinin supplement use include 8 cases of liver dysfunction, neurological adverse events that are likely related to the use of artemisinin.

- Potential artemisinin-induced hepatotoxicity/drug-induced liver injury (DILI) in 6 cases where abnormal liver function tests (LFTs), including elevated bilirubin was seen.
CAERS Cases of Liver Injury

• In 3 cases, only artemisinin was ingested; liver biopsy in 2 cases – causality suggestive of potential for DILI. Artemisinin doses unclear; appear to be 2 – 8 mg/kg for about 2 weeks or longer

• In 2 other cases, Tricycline (artemisinin + berberine as well as grapefruit citrus seed extract + black walnut hulls) ingested and in 1 other case, artemisinin ingested for babesiosis; causality suggestive but not entirely clear given confounders

• Temporal relationship, positive dechallenge, major elevations of liver enzymes and bilirubin, liver biopsy findings

• Toxicity may be associated with larger doses and longer durations than typical malaria treatment doses (4 – 6 mg/kg for 3 days)
## CAERS Cases Associated with Artemisinin

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Use</th>
<th>Dose of artemisinin</th>
<th>Onset of AE</th>
<th>Adverse Event</th>
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</thead>
<tbody>
<tr>
<td>2</td>
<td>M</td>
<td>67</td>
<td>Prostate Cancer</td>
<td>?</td>
<td>Approximately 4 weeks</td>
<td>Hepatotoxicity</td>
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<td>Malaria Prophylaxis</td>
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<td>Babesiosis</td>
<td>?</td>
<td>90 days</td>
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<td>M</td>
<td>?</td>
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<td>15 capsules/day of Tricycline</td>
<td>1 month</td>
<td>Hepatotoxicity</td>
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<td>?</td>
<td>Parasite Cleansing</td>
<td>90 capsules over 2 weeks of Tricycline</td>
<td>2 weeks</td>
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<td>Malaria Prophylaxis</td>
<td>200 mg twice a day</td>
<td>2 weeks</td>
<td>Hepatotoxicity</td>
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</table>
Adverse Events: Clinical Trials and Labeling

• Adverse events associated with artemisinin and its derivatives:
  – Neurotoxicity: Dizziness, tinnitus, vertigo, nystagmus, ataxia, dysarthria, paresthesia
  – GI toxicity: Nausea, vomiting, diarrhea
  – Hematotoxicity: Transient reticulocytopenia, neutropenia, post-treatment hemolysis
  – Hypersensitivity: Anaphylaxis, urticaria, angioedema, bullous skin rash
  – Hepatotoxicity: Potential Drug-Induced Liver Injury (DILI)
Case Reports: Hepatotoxicity

- 2 case reports of potential artemisinin-induced hepatotoxicity in patients with no risk factors (concomitant medications, viral serology, autoantibodies, obstructive processes)

- Case 1: 43 year old female
  - Normal LFTs 6 months prior
  - Took 125 mg artemisinin orally 2-3 times per day for general health maintenance
  - After 6 weeks, developed hepatitis;
    - ALT = 675 U/L,
    - AST = 175 U/L,
    - Total bilirubin = 15.4 mg/dL
  - Liver biopsy (1 week later) - cholestatic hepatitis with portal and lobular inflammation
  - Positive dechallenge (elevated LFTs resolved) after discontinuing artemisinin
Case Reports: Hepatotoxicity

• Case 2: 52 year old male
  – Normal LFTs 5 months prior
  – Took 100 mg artemisinin, 2 capsules orally 3 times per day (dose 7.5 mg/kg/day) for unidentified protozoal infection
  – After about 1 week, developed hepatitis;
    • ALT = 898 U/L,
    • AST = 280 U/L,
    • bilirubin = 3.1 mg/dL
  – Positive dechallenge (elevated LFTs resolved) within about 2 weeks of discontinuation

• In both cases:
  – Temporal relationship
  – Positive dechallenge
  – Greatly elevated liver enzymes and bilirubin
  – No risk factors suggest causal relationship between artemisinin ingestion and the potential for liver injury
Safety Conclusion

• Artemisinin and the derivatives are generally considered safe and well-tolerated as anti-malarial therapy for short term treatment.

• Severe toxicities in animal studies, such as neurotoxicity, embryotoxicity, and hematological toxicity, are not observed in short term human studies.

• Based on case reports, FAERS & CAERS data, higher doses and longer durations of treatment appear to cause drug-induced liver injury. Hepatotoxicity may be dose-related, may be idiosyncratic, or both.

• Safety of artemisinin for long-term/chronic use has not been fully evaluated.
• Artemisinin
  – Active against asexual erythrocytic forms of *Plasmodium falciparum* and *P. vivax*
  – Inactive against extra-erythrocytic forms
• Artemisinin and its derivatives have an inhibitory effect via endoperoxide bridge when used at high doses in rodent models against:
  – *Schistosoma mansoni*
  – *S. haematobium*
  – *S. japonicum*

• Artemisinin derivatives have an inhibitory effect in animal models via endoperoxide bridge against non-schistosomiasis helminthic infections, for example:
  – *Fasciola hepatica*
  – *Clonorchis sinensis*
  – *Echinostoma caproni*
Nonclinical in vitro and in vivo studies suggest that artemisinin and its derivatives may affect different steps of Toxoplasma gondii’s life cycle – by affecting calcium homeostasis and inhibiting replication, growth and attachment to host cells.
In gastric ulcer treatment, artemisinin derivatives appear to increase prostaglandin levels in gastric mucosa and exhibit bactericidal activity against *Helicobacter pylori* in rodents.

In cancer, artemisinin and its derivatives are proposed to decrease cell growth, proliferation & metastasis perhaps via:

- Endoperoxide bridge (reactive oxygen species)
- Alkylating agents (apoptosis)
- Down-regulation of vascular endothelial growth factor (inhibiting angiogenesis)
Effectiveness: Malaria

- Historically, artemisinin has been used in the treatment of malaria.
- Artemisinin and derivatives have a rapid onset of action but a short half-life.
- Per WHO guidelines, artemisinin derivatives are used in combination with longer-acting drugs that have slower onset of activity; combination therapy believed to offer rapid and complete eradication of the parasite & prevent drug resistance.
- In the United States:
  - Coartem (artemether/lumefantrine) is the only artemisinin derivative-containing antimalarial drug approved by FDA.
  - Intravenous artesunate not marketed; available from CDC.
- Prophylaxis of malaria by artemisinin derivatives is not recommended (CDC).

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Effectiveness: Schistosomiasis

- Schistosomiasis - waterborne helminthic infection, affects 200 million people worldwide, uncommon in the US. Common types – S. mansoni, S. haematobium, S. japonicum
- Based on mechanisms of action, it has been hypothesized that artemisininin derivatives (targeting eggs/juvenile worms) in combination with praziquantel (targeting adult worms) may have complementary modes of action
- No clinical trials on artemisininin in the treatment of schistosomiasis
- Based on clinical trials for artemisininin derivatives, it appears that
  - Artemisininin derivatives generally in combination with praziquantel (PZQ) may have prophylactic and treatment effect against 3 common types of schistosomiasis; as monotherapy, appear to be ineffective for prophylaxis & treatment
Effectiveness: Other Helminthic Infections

• Infections included in studies: trematodes (e.g., clonorchiasis, fascioliasis, opisthorchiasis) and nematodes (e.g., ascariasis, filariasis)
• Infections uncommon in United States
• One study evaluating artemisinin, 5 studies evaluating artemisinin derivatives
  – In a pilot study comparing PZQ to artemisinin for 5 days in clonorchiasis, artemisinin was not effective compared to PZQ
  – 5 studies evaluating artemisinin derivatives for fascioliasis, opisthorchiasis, microfilaria, intestinal helminths compared to other treatments; artemisinin derivatives not found to be efficacious
• No evidence that artemisinin and its derivatives are efficacious in treating non-schistosomiasis helminthic infections
Effectiveness: Toxoplasmosis

- Toxoplasmosis is a protozoal infection caused by intracellular parasite, *Toxoplasma gondii*.

- Infection occurs through ingestion of undercooked meat from infected animals, by contact with feces from infected cats, or congenitally via placental transfer from mother to fetus.

- No clinical studies were found that assess artemisinin or its derivatives in treating *T. gondii*.
Effectiveness:
Gastric Ulcers and Cancer

Gastric Ulcers
• No clinical studies found that assess the efficacy of artemisinin or its derivatives in the treatment of gastric ulcers

Cancer
• No clinical studies found that assess the efficacy of artemisinin in the treatment of cancer
• Pilot clinical studies and case reports assessing artemisinin derivatives and Artemisia annua for cancer treatment:
  – Reports contain insufficient information to support the usefulness of artemisinin derivatives in cancer treatment
  – Synergistic toxicity, drug-drug interactions would be expected to occur if artemisinin derivatives were added to current treatment regimens
Effectiveness: Approved Therapies

Malaria
• Multiple FDA-approved drug products indicated for treatment and chemoprophylaxis of malaria including
  – Atovaquone-proguanil, artemether-lumefantrine, chloroquine phosphate, halofantrine, hydroxychloroquine sulfate, mefloquine hydrochloride, primaquine, pyrimethamine, sulfadoxine, quinidine sulfate, quinidine gluconate, quinine sulfate, sulfadiazine, doxycycline

Helminthic Infections
• Praziquantel is FDA-approved and indicated for the treatment of infections from all species of Schistosoma for all forms of schistosomiasis, as well as for infections from Clonorchis sinensis/Opisthorchis viverrini

Protozoal Infections
• Pyrimethamine and sulfadiazine are FDA-approved and indicated for the treatment of toxoplasmosis

Gastric Ulcers and Cancer
• Multiple FDA-approved drug products are indicated for the treatment of gastric ulcers and cancer
Effectiveness Summary: Malaria

• Artemisinin has been used for the treatment of malaria but is not currently recommended as part of WHO recommended combination therapy to treat malaria

• Artemisinin derivatives are used in the treatment of malaria as part of WHO recommended artemisinin combination-based therapies with other anti-malarial drugs

• Because of their short half-life and potential for drug resistance, artemisinin and its derivatives should not be used as monotherapy

• Artemisinin and its derivatives are not recommended for prophylaxis of malaria because of concerns regarding resistance
Helminthic Infections

- Some evidence suggests that artemisinin derivatives in combination with other therapies may improve clinical response in the treatment of schistosomiasis
- Limited data do not support use for other helminthic infections

Protozoal Infections

- No studies on the use of artemisinin or its derivatives in the treatment of *T. gondii* in humans
Effectiveness Summary (3)

Gastric Ulcer
• No studies on the use of artemisinin or its derivatives to support the use of artemisinin as anti-gastric ulcer therapy

Cancer
• Limited reports regarding use of artemisinin derivatives in the treatment of some cancers; insufficient information to support use as anti-cancer treatment
Historical Use in Compounding

- Insufficient information available to determine whether and/or how long artemisinin has been used in pharmacy compounding in the United States.

- Based on internet searches, artemisinin does not appear to be available as a compounded product in the United States.

- Artemisinin is listed in the Chinese Pharmacopoeia and is available in combination with piperaquine or naphthoquine through Chinese manufacturers.

- Artemisinin is available as a dietary ingredient in dietary supplement products.

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Important Considerations

• Artemisinin is physically and chemically well characterized and is stable under ordinary storage conditions

• Artemisinin is metabolized via the cytochrome P450 enzyme system; implications for drug interactions when used for repetitive daily therapy

• Elevations of transaminases and bilirubin in patients taking artemisinin for longer than the several day regimen to treat malaria
Important Considerations (2)

• Artemisinin derivatives are an effective therapy for the treatment of malaria when used in combination with other therapies; should not be used for prophylaxis because of concerns related to the development of resistance

• Artemisinin has not been shown to be an effective therapy for non-schistosomiasis helminthic infections, gastric ulcer disease and cancer

• There is insufficient information to determine how long artemisinin has been used in pharmacy compounding
Recommendation

A balancing of the four evaluation criteria weighs **against** Artemisinin being added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act.
Oral Solid Modified Release Drug Products That Employ Coated Systems (MRC)

Pharmacy Compounding Advisory Committee Meeting
May 8-9, 2017

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Overview of Presentation

• MRC background

• Evaluation criteria considered in formulating a recommendation as to whether oral solid Modified Release drug products that employ Coated systems (MRC) are demonstrably difficult to compound:
  – Complex formulation
  – Complex drug delivery mechanism
  – Complex dosage form
  – Complex characterization and control of bioavailability
  – Complex compounding processes
  – Complex physicochemical or analytical testing

• Recommendation
MRC Background

- USP Chapter <1151> definition of modified-release:
  - “A dosage form with a drug substance release pattern that has been deliberately changed from that observed for the immediate-release dosage form of the same drug substance.”

- For the purposes of this presentation and our review, FDA defines MRC as oral solid modified release drug products that consist of an active ingredient-containing core enclosed within a polymeric coating.

- These coated systems are designed to release active ingredient at specified rates, patterns, and/or onsets through the gastrointestinal (GI) tract.

- MRC are designed to produce systemic or local action.
MRC Background (2)

MRC Diffusion and/or Enteric Systems:
- These systems’ basic physical attributes include a hydrophilic and/or water-insoluble polymeric coating enclosing a whole tablet core or a subunit core of active ingredient and excipient.
- The dosage form may be a single coated tablet or a multiparticulate tablet or capsule consisting of a number of smaller coated discrete subunits (often called beads, pellets, or spheres).
MRC Osmotic Systems:

- These systems’ basic physical attributes include a semi permeable polymeric membrane coating which encloses a compressed core composed of active ingredient, osmotic agent, and other excipients.

- Osmotic systems have one or more mechanical or laser drilled release orifices through which solutions or suspensions of active ingredient are released at a specific rate over time.
Not Considered MRC: Oral Solid Modified Release Drug Products That Do Not Employ Functional Coating Systems

Hydrophilic, hydrophobic or inert polymeric matrix systems:

- For these systems, the finished dosage form is prepared by mixing active ingredient with polymer followed by either filling into a capsule or compressing into a tablet.

- These systems consist of a polymer matrix that controls the release rate of an embedded active ingredient.

- For the purposes of our review and this presentation, the FDA does not consider matrix systems that are not coated to be MRC and has not yet evaluated them.
MRC Complexity Overview

MRC Characteristics

- Specialized raw material selection and control
- MRC design
- Distinctive manufacturing processes
- Unique in-process and final control measures

Quality Product

- Release of active ingredient at specific rates, patterns, and onsets through the GI tract
- Ensure product safety
- Ensure product efficacy
MRC Have Complex Formulations

• MRC have complex formulations in order to release a specified amount of active ingredient to a specific region of the GI tract over a specified period of time, for a given therapy.

• Release of active ingredient is influenced by:
  - complex characteristics of, and complex relationships between, active ingredient and excipient.
  - batch-to-batch variability of active ingredient and excipient.

• These factors make it difficult to maintain intended performance of MRC throughout its residence in the GI tract and may affect its safety profile.
MRC Have Complex Formulations (2)

Active ingredient properties that impact MRC performance:

- Polymorphic form: Inadequate control may lead to varying dissolution rates, permeation rates, or unexpected interactions with other ingredients.

- Solubility: The dissolution rate and pattern may vary due to excipients’ characteristics.

- Compatibility: Interactions between active ingredient and excipient may affect stability, performance, safety, and therapeutic activity.

- Purity: The presence of degradants or other impurities may affect the safety and effectiveness.
Types of excipients:

– Excipients used in MRC can include, but are not limited to, various hydrophilic and lipophilic release limiting polymers, pore forming agents, stabilizers, osmotic agents, anti-tacking agents, cushioning agents, plasticizer, permeation enhancers, diluents, disintegrants, lubricants, and glidants.

– The characterization and control of key functional excipients are critical to the safety, efficacy, quality, and performance of MRC.
Excipient characteristics:

- The release limiting polymeric coating and release modifier can heavily impact the performance of MRC.
  - Different release limiting hydrophilic and hydrophobic polymers for coating are commercially available in various grades.
  - Each polymer has individualized raw material characteristics such as viscosity profiles, impurity profiles, solvent/dispersant systems, molecular weight distribution, selected cross linkers, percentage of crosslinking, and functional groups.

- Excipients, individually and collectively, influence the release mechanism and overall product performance.
MRC Have Complex Formulations (5)

Excipient characteristics (2):

- Osmogens can widely affect the performance of osmotic MRC.
  - Osmogens are dissolved into the GI fluid once the fluid penetrates the osmotic pump through the semipermeable polymeric membrane coating, creating an increase in osmotic pressure within the pump.
  - Oftentimes, combinations of osmogens are used to achieve a specified osmotic pressure inside the system.
  - Each osmogen has individualized raw material characteristics such as particle size, wicking pressure, solubility, charge intensity, and impurity profiles.
Conclusion

– MRC are formulated from diverse ingredients with specific chemical and physical properties to ensure product performance.

– MRC require a predictable and controllable composition to exhibit consistent functionality and stability.

– If MRC are not produced correctly, sub-or supra-therapeutic release, GI mucosal irritation, and variability in performance within and/or across batches may occur.

The complexity of MRC formulations presents demonstrable difficulties for compounding
MRC Have a Complex Drug Delivery Mechanism

Factors influencing the release rate and pattern of the active ingredient from MRC:

- Thickness of the release modifying polymeric coating
- Distribution of the pore forming agents
- Thickness and surface area of the active ingredient containing core
- Layering pattern of polymer, core, and cushioning agent
- Design and components of the extragranular matrix
- Compaction characteristics
- Dimensions and distribution of the delivery orifices
- Physical distribution of osmogens and wicking agents
- Design of the pushing matrix of osmotic pump
MRC Have a Complex Drug Delivery Mechanism (2)

• For enteric MRC systems:
  – The polymeric coating dissolves to expose active ingredient at a predetermined pH, present at certain regions of the GI tract.

• For diffusion MRC systems:
  – Active ingredient is diffused through a network of pores and channels within the polymeric coating at a specified onset and rate.

• For osmotic MRC systems:
  – Active ingredient is released at a specified onset and rate through a precise orifice at the surface of the polymeric coating.
Conclusion

– The mechanism by which active ingredient is released from the MRC throughout the GI tract is complex because:
  
  • it requires the design and formation of a system that delivers a specific amount of active ingredient per unit time and in some cases in specific regions of the GI tract (e.g., enteric coated MRC).
  • the active ingredient release profile is impacted by several factors which may adversely affect safety and efficacy of MRC product.

The complexity of MRC delivery mechanisms presents demonstrable difficulties for compounding.
MRC Are Complex Dosage Forms

- MRC have complex dosage forms because, as previously explained, they have complex formulations and complex mechanisms of drug release.
- To achieve proper performance, MRC dosage forms require:
  - characterization, specialized selection, and precise control over the raw materials.
  - controlled manufacturing processes.

The complexity of MRC dosage forms presents demonstrable difficulties for compounding.
Bioavailability of MRC is Difficult to Characterize and Control

Small changes in MRC performance characteristics can significantly impact bioavailability, and in turn the safety and effectiveness of the product.

– For systemically acting MRC products, characterizing pharmacokinetic behavior of such MRC formulations is critical.

– For locally acting MRC products, drug activity is often assessed using *in vitro* testing and pharmacodynamic studies, or by evaluating clinical endpoints.
Bioavailability of MRC is Difficult to Characterize and Control (2)

• Several physiological factors within the GI tract impact active ingredient bioavailability.
  – e.g., fed and fasted states, gastric emptying rates, mucosal secretions, salt concentrations, pH, bile acid and phospholipid secretions, and variations in the anatomical sites of the GI tract

• In developing MRC for the purposes of seeking FDA approval, sponsors typically perform a multitude of studies, including \textit{in vivo} (e.g., pharmacokinetic studies) and \textit{in vitro} (e.g., dissolution testing) assessments to demonstrate and ensure proper product performance.
Bioavailability of MRC is Difficult to Characterize and Control (3)

Conclusion

– Subtle changes to MRC components, composition or manufacturing processes could significantly impact the drug product’s performance characteristics, which may in turn influence bioavailability.

– In general, *in vitro* assessments alone are insufficient to accurately predict bioavailability and overall clinical effects. Rather, *in vivo* assessments are needed.

MRC are complex systems for which bioavailability is difficult to characterize and control and therefore present a demonstrable difficulty for compounding.
MRC Involve Complex Compounding Processes

- MRC require complex and specialized production processes, including the use of specialized equipment, to yield predictable delivery of drug products within and across batches.

- Specialized production processes include:
  - Mixing of active ingredient with excipient to achieve blend uniformity
  - Layering/coating of polymeric coats around the active ingredient containing cores
  - Filling the specially designed and coated subunits into capsules or compressing the subunits into tablets
  - For osmotic MRC, creating an accurate and precise delivery orifice after the coating process
MRC Involve Complex Compounding Processes (2)

• Mixing:
  – The overall unit-to-unit and batch-to-batch blend uniformities are dependent on the physical characteristics (e.g., flow, density, surface charge, particle size, particle shape, and volume fractions) of the MRC components.
  – Blend uniformity is also dependent on various mixing parameters, such as mixing time, mixing principle, mixer dimensions and shape, and impeller speed.
  – For multiparticulate diffusion systems, the ratio of the blend for filling into capsules or compression into tablets is in turn dependent on the ratio of the coated subunits of the active ingredient and the extragranular excipient mixture.

• Incomplete, excessive, or variable mixing can lead to MRC not achieving proper performance.
Coating and drying:

– To ensure uniform thickness of continuous coats around the solid particles, it is critical to employ automated coating equipment.

– The coating process involves a method of successive layering and drying according to a specified design, in order to achieve the desired release rate and pattern.

– Varying thickness, weight gain, residual solvent, and/or moisture level of each coating layer can directly impact the active ingredient content and release characteristics.
MRC Involve Complex Compounding Processes (4)

Coating and drying (2):

- Numerous release-limiting and other modifying materials are commercially available with various physicochemical properties.
- The drying process during fluidized bed processing is a critical step in controlling residual solvents and volatile polymeric impurities.
MRC Involve Complex Compounding Processes (5)

• Compaction:
  – For subunits that are compressed into tablets, compaction is typically performed on an automated tablet press equipped with precise controls for applying compaction and ejection forces that define the dimensions and weight of the tablet.
    • Compaction forces above certain predefined limits can lead to fractures and dose dumping
    • Compaction forces below predefined limits can lead to fragile, friable, and/or non-consistent tablets
  – For osmotic systems, appropriate compaction is critical for maintaining a consistent wicking action of osmotic agent, which is crucial to product performance, effectiveness, and safety.

• Filling:
  – For subunits that are filled into capsules, changes in the loading fractions of varying particulates can result in undesirable release rates and patterns.
Creation of a delivery orifice for osmotic systems:

– Delivery orifices in osmotic systems are often created mechanically or by laser.

– For laser drilled orifices, the size and depth of the orifice are controlled by the laser beam parameters, such as laser power, firing pulse, and duration.

– Drilling parameters are individually selected based on the specific osmotic system.

– The size of the delivery orifice must be optimized in order to control the predetermined release rate and pattern of release.
MRC Involve Complex Compounding Processes (7)

Conclusion

– The compounding processes for MRC are complex because specialized equipment and appropriate in-process controls are critical for production.

– Improper selection or control of any of these production steps will likely affect MRC performance, effectiveness, and safety.

Production of MRC involves complex processes that present demonstrable difficulties for compounding.
MRC Necessitate Complex Testing

- Extensive characterization and developmental studies on the specific formulation, functional properties, and production processes are necessary to develop the specifications and in-process controls that should be used to ensure that the product will perform at predetermined specifications.

- A large number of complex tests are needed to ensure satisfactory and consistent performance of MRC, such as:
  - Raw material testing
  - In process controls and tests
  - Product quality testing
  - Stability testing
Raw Materials Testing

- Rigorous qualification of raw materials (e.g., release controlling materials, osmogens, pore forming agents) is important for the safety and effectiveness of MRC.
  - For example, raw material properties, such as viscosity, swelling ratio, dissolution, and impurity content, should be tested.

- Commercially available raw materials could vary from manufacturer to manufacturer.
MRC Necessitate Complex Testing (3)

Product Quality Testing

– USP general tests for *Oral Drug Products-Product Quality* are related to the description, identification, assay, and impurities for oral dosage forms.
  • Specifically for tablets, Chapter <2> identifies tests for volatile contents, disintegration, friability, breaking force and uniformity, as well as specific tests for coated tablets.

– However, precise methods for many of these tests are not usually articulated. Rather, only general methods for testing the dissolution rate and pattern are described.

– Important active ingredient release tests for MRC include *in vitro* dissolution, assay, content uniformity, disintegration, friability, impurity, and residual solvent testing.
  • Sophisticated equipment and specialized methods are critical for these tests.

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Product Quality Testing (2)

– In process controls and tests:
  • Precise control of production processes is necessary to ensure proper performance of MRC. For example, loss on drying and percent of weight gain are critical for the coating processes.

– *In vitro* dissolution testing:
  • *In vitro* testing may be utilized to ensure batch-to-batch uniformity.
  • There are multiple compendial and non-compendial methods and technical nuances for dissolution testing.
    – Nuances include a specific apparatus design, volume and composition of the medium, stirring rate, temperature, and sampling schedule.
  • Variations in any of these parameters can significantly impact the meaningfulness of the result.
Stability Testing

– Product quality stability testing is critical to ensure MRC stability throughout the dosage form's shelf-life and in-use period after dispensing to the patient.

– The selection of conditions for stability testing (e.g., storage time, containers and closures, open or sealed containers, presence or absence of desiccants, and fill volume) can affect the results of product stability tests.
Conclusion

– MRC require complex analytical testing and procedures to ensure accurate characterization of raw material, product quality/performance, and stability.
– The appropriate tests are difficult to develop, validate, and perform routinely.
– Proper testing involves highly specialized equipment and analysts that have received considerable training.

MRC require complex testing that presents demonstrable difficulties for compounding
Risks and Benefits to Patients

- FDA-approved MRC are currently used for the management of severe pain, hypertension, diabetes, attention deficit hyperactivity disorder, Parkinsonism, epilepsy, and schizophrenia.

- These products are monitored by FDA to identify drug safety concerns and recommend actions to improve product safety and to protect the public health.

- There is currently an adequate supply of approved MRC on the market and thus there is limited, if any, benefit to expanding the market to include compounded MRC.
Risks and Benefits to Patients (2)

- As discussed, MRC design and the relationship between excipient and active ingredient directly impacts release rate and pattern, product performance, effectiveness, and safety.
  - Substituting or removing excipients is likely to adversely impact the product performance.

- Precise and consistent quality control of raw materials, manufacturing processes, and the final product is essential for predictable and reproducible active ingredient release, drug product performance, and safety profile.

Any potential benefit that may be derived would be outweighed by the risks associated with allowing a compounder to attempt to produce these complex drug products.
Recommendation

• FDA believes that MRC present demonstrable difficulties for compounding that reasonably demonstrate, and are reasonably likely to lead to, an adverse effect on the safety or effectiveness of this category of drug products.

• Taking into account the risks and benefits to patients, FDA believes MRC should be included in the Difficult to Compound List under sections 503A and 503B of the FD&C Act.