Quinacrine Hydrochloride

Pharmacy Compounding Advisory Committee Meeting
March 8, 2016

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Outline

• Quinacrine physical and chemical characterization
• Regulatory and marketing history
• Safety
  – Nonclinical evidence
  – Clinical evidence
• Use-specific discussion and recommendation
  – Division of Anti-Infective Products:
    • Infectious Uses
  – Division of Pulmonary, Allergy, and Rheumatology Products:
    • Lupus
  – Division of Bone, Reproductive, and Urologic Products:
    • Intrauterine sterilization
Quinacrine hydrochloride: Physical and Chemical Characterization

- Structure differs slightly from chloroquine
- Available in highly pure form (97-99%)
- Yellow powder; very stable
Regulatory and Marketing History

- Quinacrine tablets, as a single ingredient product, were introduced as an antimalarial drug in the 1930s but have never been formally FDA approved.
- Unapproved quinacrine tablets were marketed until 1995 for the treatment of giardiasis, tapeworm, and malaria and were discontinued due to decrease in demand.
- Quinacrine was approved in combination with hydroxychloroquine and chloroquine (Triquin tablets) for lupus in 1958; Triquin was withdrawn in 1973 for insufficient evidence of efficacy.
- Quinacrine injection was FDA approved in 1964 for ascites. In 2003 the manufacturer notified FDA that it was no longer marketed.
- Quinacrine is not currently approved in the United States, but oral quinacrine is compounded to a limited extent for lupus.
Other Historical Use of Quinacrine

- As injection for malignancy-associated pleural effusions
- Orally for rheumatoid arthritis
- As an intrauterine slurry and pellets for female sterilization
Quinacrine Safety: Nonclinical Evidence

- No safety pharmacology studies available
- Possible cardiac and hepatic toxicity in rats in repeat dosing
- Positive studies for mutagenicity (Ames; Chinese hamster ovary chromosomal aberrations); quinacrine is a known mutagen
- Readily crosses placenta to fetus; administration to pregnant rats and monkeys associated with fetal death
- Carcinogenic in rats when introduced in uterus
## Safety: Clinical Evidence*

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reactions **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>Yellowish discoloration, eczematous rash, worsening of psoriasis, lichen planus</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, diarrhea, vomiting, abdominal cramping</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Aplastic anemia with chronic use, porphyria</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Psychosis, restlessness, insomnia; can occur with short term use</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Elevated liver function tests; hepatitis</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Retinopathy but less than similar agents; corneal edema/deposits</td>
</tr>
</tbody>
</table>

**Many adverse reactions are dose- and duration-dependent**

*From published literature and labeling*
Special Safety Concerns

• Aplastic anemia
  – Approximate rate is 1/50,000
  – Reversible; historic mortality rate is 50%
  – Mostly associated with doses greater than those used for the treatment of lupus, i.e., 100 mg daily

• Psychosis, especially in patients over 60 years of age

• Rashes including lichenoid reactions associated with subsequent development of squamous-cell skin cancer

• Reproductive tract malignancies – relevant to intrauterine use
Use-Specific Discussion and Recommendations

Division of Anti-Infective Products: Infectious Uses

Division of Pulmonary, Allergy, and Rheumatology Products: Lupus

Division of Bone, Reproductive, and Urologic Products: Intrauterine Female Sterilization
Infectious Uses of Quinacrine

- **Malaria**
  - Quinacrine has been supplanted by more efficacious and less toxic drugs and is no longer used to treat this condition

- **Giardiasis**
  - Quinacrine has been supplanted by tinidazole (approved), nitazoxanide (approved), and metronidazole (off-label)
  - There are published cases of successful use of quinacrine for giardiasis nonresponsive to nitroimidazoles outside the United States but the relevance of these data to the United States is uncertain

- **Tapeworm infection**
  - Quinacrine has been supplanted by praziquantel and is no longer used in the United States to treat this condition
Infectious Uses:
Division of Anti-Infective Products
Recommendation for 503A

- **We do not recommend** that quinacrine hydrochloride be included on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).
  - Physically and chemically well characterized.
  - Significant historical use of quinacrine hydrochloride, but unknown history to what extent the compounding was for infectious disease uses.
  - Benefits do not outweigh risks for infectious disease uses.
  - Potential use is for non-life-threatening infections for which alternative treatments are available.
  - Significant safety concerns including aplastic anemia, psychosis, and dermatologic effects.
  - Distribution via compounding will not be associated with labeling providing important safety information.
  - Use under an IND could allow for provision of safety information in setting of research use/individual cases.
Use-Specific Discussion and Recommendations

Division of Anti-Infective Products: Infectious Uses

Division of Pulmonary, Allergy, and Rheumatology Products: Lupus

Division of Bone, Reproductive, and Urologic Products: Intrauterine Female Sterilization
Systemic Lupus Erythematosus (Lupus)

- 1.5 million Americans are diagnosed with lupus
- Women are affected 10x more frequently than men
- African Americans, Latinos, Asians, and Native Americans are affected 3x more frequently than Caucasians
- Prototypic autoimmune disease
  - Systemic involvement in 70% of cases affecting all major organs
  - Cutaneous lupus accounts for 10% of lupus cases
- Unmet medical need
Lupus: Background

Disease management largely consists of pharmacologic therapy with immunosuppressant drugs

• FDA-approved therapies:
  – Corticosteroids
  – Hydroxychloroquine
  – Belimumab (Benlysta)

• Off-label therapies:
  – Other antimalarials (quinacrine, chloroquine)
  – Methotrexate
  – Mycophenolate mofetil
  – Cyclosporine
  – Cyclophosphamide
Lupus: History of Antimalarials

• Antimalarials have been used to treat lupus since 1894, when Payne first used quinine

• Quinacrine was first used in discoid lupus by Prokoptochouk in 1939 and Sorinson in 1941
  – The first English language report of its use in lupus by Page in 1951 (Lancet) generated much interest and a series of large scale studies in the 1950’s (a total of 20 clinical trials from 1939 to 1961)

• The introduction of hydroxychloroquine as an alternative antimalarial in 1955 resulted in a decrease in interest in quinacrine by the late 1950’s

Lupus: Efficacy

• Meta analyses of large case series involving 771 lupus patients treated with quinacrine between 1940 to 1961 described clinical improvement in 73-85% of treated patients:
  – Doses were 200 to 300 mg qd initially, tapering to 100 mg qd maintenance, with response within 1 to 2 weeks
  – Starting at 100 mg qd improved tolerability and response was seen in 3 to 4 weeks

• Multiple prospective studies support the clinical efficacy of combinations of quinacrine, chloroquine, or hydroxychloroquine for treatment of cutaneous lupus erythematosus.

• Quinacrine 100 mg/d is recommended treatment for the treatment of systemic and cutaneous lupus in medical references and treatment guidelines:
  – Rheumatology textbooks, review articles, UptoDate, Medscape
Lupus: Risk-Benefit of Treatments

- Systemic manifestations of lupus can be serious and organ/life-threatening; skin manifestations can be disfiguring.

- Currently used therapies are associated with life-threatening and serious adverse events including death, malignancy, lung fibrosis, aplastic anemia, bone marrow suppression, opportunistic infections, and avascular necrosis.

- Hydroxychloroquine is FDA-approved for the treatment of lupus with labeled adverse events of death, irreversible retinal damage, aplastic anemia, agranulocytosis, anemia, and thrombocytopenia.
Lupus: Quinacrine Conclusions

• Many older antimalarials (including quinacrine, chloroquine, and hydroxychloroquine) have been studied in lupus and are considered effective.

• Although antimalarials have many overlapping toxicities, quinacrine differs in terms of the risk of retinopathy, which is dose-related and irreversible with chloroquine (CQ) and hydroxychloroquine (HCQ)
  – Addition of quinacrine (i.e., 100 mg qd) to lower doses of CQ and HCQ provides a way for clinicians to maximize antimalarial therapy without increasing the risk of retinopathy.

• Quinacrine does have dose-related toxicity of yellow skin discoloration and rare idiosyncratic events of aplastic anemia.
  – These are not inconsistent with the level of risk with other lupus treatments.
Lupus Use:
Division of Pulmonary, Allergy, and Rheumatology Products Recommendation for 503A

• We **recommend** that quinacrine hydrochloride be placed on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act
• Physically and chemically well characterized
• Long history of use and is currently compounded for lupus patients
• Safety profile of quinacrine not inconsistent with that of other lupus treatments
• Evidence in scientific literature supports efficacy and therapeutic need
Use-Specific Discussion and Recommendations

Division of Anti-Infective Products: Infectious Uses

Division of Pulmonary, Allergy, and Rheumatology Products: Lupus

Division of Bone, Reproductive, and Urologic Products (DBRUP): Intrauterine Sterilization
Outline

• Quinacrine for intrauterine sterilization
• Regulatory history
• Other guidance
• DBRUP recommendation
Intrauterine Sterilization: Quinacrine

• 252 mg (7 pellets) of quinacrine placed into the uterine cavity with the aim of causing fibrosis and occlusion of the fallopian tubes; procedure repeated 2 to 4 times, one month apart

• Used widely throughout the world in the latter half of the 20th century
  – over 140,000 quinacrine sterilizations performed from 1977-2000*

• Procedure subsequently banned in a number of countries due to concerns about lack of informed consent and about long-term safety

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**Intrauterine Sterilization: Efficacy**

- Majority of efficacy data are based on follow-up of women in developing countries; almost no randomized or controlled clinical trials
  - Data often collected in a subset of subjects; where reported, 10-20% of subjects lost to follow up
  - Not consistently based on serum or urine pregnancy testing
  - Various dosing regimens used
- Reported pregnancy rates (Sokal et al., 2008) range from:
  - 0.3 to 3.3% in first year
  - 1.1 to 10% over five years
  - 4.3 to 12.1% over 10 years
- These compare unfavorably with surgical sterilization or IUDs
Intrauterine Sterilization: Regulatory History

• FDA conducted a safety assessment and a health hazard evaluation (HHE) in 1998 of a kit for intrauterine insertion of quinacrine pellets for female sterilization and identified the following concerns:
  – Possible carcinogenicity
  – Lack of PK data with possible long-term exposure of the endometrium following administration
  – Failure of cytotoxic agents to completely destroy the endometrium, and neoplastic transformation of residual endometrial cells
  – Other possible safety issues including uterine perforation during insertion, intraperitoneal leakage of dissolved quinacrine, ectopic pregnancy, etc.

• FDA issued a warning letter in 1998, concluding that female sterilization is an unsafe use of the drug product, quinacrine pellets
  – Distribution of the unapproved pellets for this use to be halted immediately, with all product to be removed from the market
Regulatory History (cont.)

• Subsequent to the 1998 HHE evaluation, a rat carcinogenicity study of intrauterine quinacrine was conducted. The authors stated (Cancel et al., 2010):
  – *We conclude that two doses of quinacrine administered approximately 21 days apart into the uterus of young sexually mature rats at dose levels ≥ 70 mg/kg increased the lifetime risk of tumor development in the reproductive tract. The types of tumors that developed were mostly uncommon for this strain of rat. The incidence of these tumors was dose-related and was significantly increased at a local quinacrine dose that was a small multiple (8x based on a mg quinacrine/g uterus basis) of the human dose of quinacrine used for non-surgical female sterilization.*
Intrauterine Sterilization: Other Guidance on Use of Quinacrine

- In 2008, a World Health Organization (WHO) Technical Panel reviewed the available nonclinical and clinical data on quinacrine as a sterilizing agent and concluded:
  - “Until the totality of safety, effectiveness and epidemiological data has been reviewed, quinacrine should not be used for non-surgical sterilization of women in either clinical or research settings.”*

- To date, this statement remains in place.

Intrauterine Sterilization: Conclusions

• There are significant safety concerns regarding the increased risk of reproductive tract malignancies with intrauterine use of quinacrine hydrochloride.

• Intrauterine quinacrine hydrochloride does not appear to provide a level of efficacy that compares favorably to other available methods of permanent female sterilization.

• Therefore, the benefit/risk profile is unfavorable.
Intrauterine Sterilization: Division of Bone, Reproductive and Urologic Products Recommendation for 503A

- We do not recommend that quinacrine hydrochloride for intrauterine administration be placed on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.

- Physically and chemically well characterized
- There is some evidence of historic use in compounding
- Serious safety concerns
- Efficacy does not compare favorably to other methods of birth control or sterilization
# Summary: Use-Specific Recommendations for the 503A List

<table>
<thead>
<tr>
<th>Uses</th>
<th>Recommendation based on balancing of evaluation factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral route of administration</td>
<td></td>
</tr>
<tr>
<td>Lupus</td>
<td>Yes</td>
</tr>
<tr>
<td>Infectious Diseases</td>
<td>No</td>
</tr>
<tr>
<td>Intrauterine route of administration</td>
<td></td>
</tr>
<tr>
<td>Intrauterine Sterilization</td>
<td>No</td>
</tr>
</tbody>
</table>
Quinacrine Hydrochloride

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March 8, 2016

Charles J. Ganley, MD
Director, Office of Drug Evaluation IV
Office of New Drugs (OND)

- Within OND, there are six sub-offices and within each sub-office there are divisions
  - Office of Drug Evaluation I  [Cardiovascular-Renal, Neurology, Psychiatry]
  - Office of Drug Evaluation II  [Metabolism-Endocrinology, Pulmonary-Allergy-Rheumatology, Anesthesia-Analgesia-Addiction]
  - Office of Drug Evaluation III  [Dental-Dermatology, Gastroenterology-Inborn Errors, Bone-Reproductive-Urologic]
  - Office of Drug Evaluation IV  [Medical Imaging, Nonprescription Drug, Pediatric-Maternal Health]
  - Office of Antimicrobial Products  [Anti-infective, Antiviral, Transplant-Ophthalmology]
  - Office of Hematology and Oncology Products  [Oncology 1, Oncology 2, Hematology, Hematology Oncology Toxicology]
Division Recommendations

- The recommendations of the divisions are based on their benefit-risk assessment for the uses being considered under the purview of their therapeutic expertise.
- For quinacrine, reviews by DAIP, DBRUP, and DPARP of information specific to each therapeutic use resulted in disparate recommendations.
- The recommendations for each use, as explained in the reviews and presentations, have been thoughtfully derived and the rationale for the recommendations are clear.
ODEIV Review

- ODEIV was assigned to review the information in each division memorandum and make an overall recommendation with the concurrence of the Director of the Office of New Drugs.
- This recommendation will represent the position of FDA on this nomination.
- The OND memo provides the rationale for the overall recommendation.
Use of Quinacrine

- Single ingredient tablet dosage form marketed in the United States under the Atabrine name but not approved; marketing discontinued in 1995
- Quinacrine has been compounded for the past 20 years or more
- In 2015, approximately 1,400 quinacrine prescriptions dispensed from U.S. outpatient retail pharmacies and long-term care settings were prescribed primarily by rheumatologists and dermatologists\(^1\)

OND Assessment of Quinacrine

- OND finds that with regard to intrauterine administration of quinacrine for sterilization and for the use of quinacrine as an anti-malarial or antiprotozoal or for the treatment of rheumatoid arthritis, there are FDA approved medications or methods that have a more favorable benefit-risk assessment.
- OND finds that for the treatment of Lupus patients, particularly those with cutaneous symptoms, there are case series supporting effectiveness and a risk profile similar to other drugs used to treat the condition.
- Quinacrine is, however, associated with serious side effects.
OND Assessment of Quinacrine

- OND is concerned that prescribers of quinacrine and patients using quinacrine may lack sufficient information about its use.
- To better ensure the safe and effective use of quinacrine, prescribing information is needed and is not provided under the framework of the 503A list.
  - Include the potential for serious and life-threatening adverse effects.
  - Include appropriate treatment monitoring and follow up.
OND Recommendation for Quinacrine

• We **do not recommend** quinacrine for the 503A bulks list because of the serious side effects associated with the use of quinacrine
  – Given the serious adverse effects and lack of an FDA approved drug label to guide safe and effective use, we cannot recommend quinacrine for inclusion on the 503A list
OND Recommendation for Quinacrine

- OND recognizes that:
  - Quinacrine has a long history of use in the treatment of patients with lupus, particularly those with cutaneous symptoms.
  - There is a population of patients with lupus that likely benefit from the treatment with quinacrine.

- OND is committed to helping the clinical community maintain the availability of quinacrine for use in well informed and managed therapeutic situations.

- We recommend that quinacrine be obtained under an IND.
Boswellia serrata extract (BWSE)

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Janet Maynard, MD, MHS
Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Boswellia serrata extract: Review Team

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Cassandra Taylor, PhD, Botanical Review Team, Office of Pharmaceutical Quality (OPQ)

Jinhui Dou, PhD, Botanical Review Team, OPQ

Charles Wu, PhD, Botanical Review Team, OPQ

Su-Lin Lee, PhD, Botanical Review Team, OPQ
Uses Evaluated

• Nominated for use in inflammatory bowel disease, rheumatoid arthritis (RA), osteoarthritis (OA), asthma, and for anti-inflammatory properties generally
• Clinical review will focus on use in OA and RA
Botanical Raw Material and Its Use

- *Boswellia* is a genus in the Burseraceae family with ~40 species
- Boswellia resin/extracts are available on U.S. market as dietary supplements
  - Oral and topical applications of Boswellia as herbal medicines are used in other parts of the world for various disease/symptom treatments (e.g., arthritis/pain)
- Multiple Boswellia resins are listed in various Pharmacopeias

<table>
<thead>
<tr>
<th>Name of Botanical</th>
<th>Description</th>
<th>Pharmacopeia</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Boswellia serrata</em></td>
<td>Oleogum resin obtained by incision or produced by spontaneous exudation from the stem and branches of <em>Boswellia serrata</em> Roxb.</td>
<td>United States, Dietary Supplements, Errata to Second Supplement to USP 37 – NF 32</td>
</tr>
<tr>
<td><em>Boswellia serrata</em></td>
<td>Extract prepared from pulverized <em>Boswellia serrata</em></td>
<td>United States, Dietary Supplements, Errata to Second Supplement to USP 37 – NF 32</td>
</tr>
<tr>
<td>Indian Frankincense/Olibanum indicum</td>
<td>Air-dried gum-resin exudate from stem or branches of <em>Boswellia serrata</em></td>
<td>European, 8.0</td>
</tr>
<tr>
<td>Olibanum</td>
<td>Dried resin exuding from the bark of <em>Boswellia carterii or Boswellia bhawajiana</em>; drug is divided into Somalia olibanum and Ethiopia olibanum</td>
<td>Chinese, 2010 English Edition, p.301</td>
</tr>
</tbody>
</table>
Chemical Composition of Boswellia

- Boswellia extracts are complex naturally derived mixtures that can vary significantly in compositions
  - Boswellic acids (e.g., 22–80%) that have been considered as useful bioactive chemical marker compounds
  - Volatile oils (e.g., 5–15%)
  - Other components, such as tirucallic acids, other acids, and polysaccharides (e.g., 10–40%)
- The overall composition in a given Boswellia extract is often unknown
- Boswellic acid analogs:
Quality Considerations (1)

• Composition of Boswellia extracts, including total content and relative proportions of the boswellic acid analogs, can differ depending on the botanical source (e.g., *B. serrata* vs. *B. carterii*) and manufacturing methods

  – Good agricultural and collection practices (GACP) to support sustainable production of Boswellia resin in native habitats (i.e., India and Ethiopia) have not been established
  – Raw materials may vary significantly in quality
  – Different manufacturing processes (including various solvent extractions) have been utilized to concentrate the boswellic acids from boswellia resins
Quality Considerations (2)

- Boswellia extracts contain multiple classes of molecules, so their composition is not well characterized and cannot be adequately controlled solely based on the analysis of boswellic acids.
- Additional raw material and manufacturing process controls are needed to ensure the quality of boswellia extracts (e.g., consistency in chemical composition).
- In conclusion, we do not consider Boswellia extract to be well-characterized and can be adequately controlled for compounding drug use from a quality perspective.
Nonclinical Assessment

**Pharmacology:** Boswellia serrata extract possesses anti-inflammatory properties, but the exact mechanism of action is unknown

**Repeat-Dose toxicity:** Rats dosed with 1,500-mg/kg/day BWSE enriched with 30% AKBA for 90 days showed no apparent toxicity

**Mutagenicity and Carcinogenicity**
- Boswellia serrata extract was not genotoxic in *in vitro* and *in vivo* testing
- Carcinogenicity has not been evaluated in animals

**Reproductive and Developmental Toxicity**
- Reproductive and developmental toxicity of Boswellia serrata extract has not been evaluated in animals, but the Chinese Pharmacopeia (2010) states that Boswellia serrata extract products are not recommended in pregnant women
Clinical Assessment: Safety (1)

Reported adverse effects/safety in published literature

- Diarrhea, abdominal pain, nausea (Abdel-Tawab 2011)
- Emmenagogue (promotion of menstrual flow), potential to induce abortion or prevent pregnancy (Basch 2004; Jadhav 2005; Kamboj 1988)
- Increase in anticoagulant effect (Paoletti 2011)
Clinical Assessment: Safety (2)

Clinical trials assessing safety

- Reported adverse events in clinical trials (Kimmatkar, 2003; Sengupta, 2008; Sengupta, 2010; Visahl, 2011; Sontakke, 2007; Chopra, 2000):
  - Epigastric and abdominal pain
  - Nausea
  - Diarrhea
  - Fever
  - Headache
  - Acidity
  - Anorexia
  - Constipation
Clinical Assessment: Safety (3)

- FDA Adverse Events Reporting System (FAERS): seven reports (including one duplicate report)
  - 3 cases from literature describing drug interactions between Boswellia and warfarin that resulted in an over-anticoagulation effect
- Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS): 208 cases
  - Spectrum of adverse event severity, including serious and life-threatening adverse events and deaths
  - All of the cases involved products containing multiple components or other medications, thus no definitive conclusions were possible
Clinical Assessment — OA: Efficacy (1)

Cochrane review (Cameron 2014): high quality evidence from two studies (85 participants) that 90 days of treatment with 100 mg of enriched Boswellia serrata extract improved symptoms compared to placebo
# Clinical Assessment — OA Studies: Efficacy (2)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Study Arms</th>
<th>Therapy Duration</th>
<th>Summary of Publication’s Efficacy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimmatkar 2003</td>
<td>BWSE (Cap Wokvel™) 333 mg tid (n=15) Placebo (n=15)</td>
<td>8 weeks</td>
<td>Statistically significant difference in severity of pain and swelling and improvement in loss of function in the BSWE treated patients compared to placebo treated patients</td>
</tr>
<tr>
<td>Sengupta 2008</td>
<td>5-Loxin® 100 mg daily (n=25) 5-Loxin® 250 mg daily (n=25) Placebo (n=25)</td>
<td>90 days</td>
<td>Statistically significant reductions in pain VAS, LFI, and WOMAC subscale scores for 5-Loxin® (100 mg and 250 mg) versus placebo</td>
</tr>
<tr>
<td>Sengupta 2010</td>
<td>5-Loxin® 100 mg/day (n=20) Aflapin® 100 mg/day (n=20) Placebo (n=20)</td>
<td>90 days</td>
<td>Statistically significant reductions in pain VAS, LFI, and WOMAC subscale scores for 5-Loxin® versus placebo and Aflapin® versus placebo</td>
</tr>
<tr>
<td>Vishal 2011</td>
<td>Aflapin® 100 mg/day (n=30) Placebo (n=30)</td>
<td>30 days</td>
<td>Statistically significant reductions in pain VAS, LFI, and WOMAC subscale scores for Aflapin® versus placebo</td>
</tr>
<tr>
<td>Sontakke 2007</td>
<td>BWSE (Cap Wokvel™) 333 mg tid (n=33) Valdecoxib 10 mg daily (n=33)</td>
<td>6 months</td>
<td>Statistically significant reductions in the 3 WOMAC subscale scores for BWSE versus valdecoxib at 7 months (1 month after stopping therapy)</td>
</tr>
</tbody>
</table>

LFI=Lequensen’s Functional Index, WOMAC=Western Ontario McMaster University Arthritis Index; VAS=visual analogue scale; tid=three times daily, 5-Loxin®=Boswellia serrata extract enriched to 30% AKBA; Aflapin®=Boswellia serrata extract enriched with AKBA and Boswellia serrata non-volatile oil
Clinical Assessment—RA: Efficacy (3)

- Four publications of studies evaluating Boswellia serrata extract for the treatment of RA identified
  - One study noted “there was no subjective, clinical, or laboratory parameter showing a clinically relevant change from baseline or difference between both groups at any time point of observation” (Sander, 1998)
  - Two studies used drugs with multiple components so it was unclear which component might be contributing to potential effects (Chopra, 2000; Kulkarni, 1992)
  - One publication reviewed results of other studies, but limited details provided and some studies included patients with diagnoses other than RA (Etzel, 1996)
  - No evidence that BSWE inhibits radiographic progression in RA
- Therefore, these studies do not provide convincing evidence for use of Boswellia serrata extract for the treatment of RA.
Clinical Assessment: Efficacy (4)

This compound is intended for the treatment of numerous conditions, including OA and RA, which are serious diseases. Numerous treatments have been approved by FDA for OA and RA after demonstration of efficacy in well-controlled trials.

Conclusion: While there are limitations to the available data, there is some evidence that Boswellia serrata extract may improve symptoms for some patients with OA. There is insufficient evidence that there is efficacy for RA. Further, there are numerous treatments for RA that have established efficacy, and there is a risk of irreversible structural damage with ineffective therapies.
Historical Use in Compounding

• Historically, Boswellia has been used for millennia throughout the world, particularly in Ayurvedic and traditional Chinese medicine.
• Various therapeutic uses, such as anti-inflammatory, analgesic, diuretic, antiseptic
General Conclusions

- Since it is a naturally-derived, botanical substance, Boswellia serrata extract’s physical and chemical characteristics can vary according to the source and extraction method.
- Cannot ensure consistent quality of bulk drug substance
- Limited safety data suggest Boswellia serrata extract is generally well tolerated.
- However, its association with terminating and preventing pregnancy is a significant safety concern given the potential use in women of child bearing potential.
- There are reports of interactions with oral anticoagulants leading to an increase in anticoagulant effect.
- Literature data suggest there may be efficacy for some OA patients, but inadequate data to support efficacy for RA.
- A number of safe and effective FDA-approved agents are available for the treatment of RA and OA.
- There is historical use of Boswellia serrata extract for a variety of conditions.
Recommendation

We do not recommend that Boswellia serrata extract be placed on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act.
Aloe vera (Freeze dried 200:1)

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David Kettl, MD
Clinical Team Leader, Division of Dermatology and Dental Products (DDDP)
Aloe vera (Freeze dried 200:1)

Pharmacy Compounding Advisory Committee Meeting
March 8, 2016

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Aloe Vera (freeze dried) 200:1 — Uses

• Nominated for “the treatment of burns, cuts, ulcers, and diabetic wounds”
• Nomination states that the substance will be used to prepare topical creams and gels at concentrations of 0.1-10%
• Nomination does not specify the basic characteristics of cuts, burns, and wounds for which Aloe vera freeze-dried 200:1 is intended, e.g., size, location, duration, and infection status, all of which are critical elements for efficacy and safety assessments of the proposed product
Botanical Raw Material and Its Use

- *Aloe vera* (L.) Burm. f. (syn. *Aloe barbadensis* Mill.) is a succulent plant species within the *Aloe* genus, which has about 500 species.
- *Aloe vera* leaf (whole leaf, gel or the inner part of the leaf) and extracts are common herbal/traditional medicines, as oral laxatives or topical agents for burns and wounds.
- Commercially available products derived from *Aloe vera* are food, dietary supplements, or cosmetic products on the U.S. market.

The Nominated Substance: Aloe vera freeze-dried 200:1

- The nomination **does not** provide a definition of “Aloe vera freeze-dried 200:1”
- The name suggests any extract or dry powder derived from whole *Aloe vera* leaf or any part of *Aloe vera* (i.e., the botanical raw material) with a concentration ratio of 200 to 1 (i.e., 200 g of *Aloe vera* botanical raw material yields one gram of the freeze dried extract/powder)
  - No solvents are specified
- “Aloe vera freeze-dried 200:1” can be “Aloe vera gel freeze-dried (200:1)” as 200 g of Aloe vera gel will typically yield 1 g of freeze dried powder
Chemical Composition of *Aloe vera*

- Majority of *Aloe vera* products are complex mixtures
  - Containing various classes of compounds: e.g., polysaccharides, anthraquinones, and organic acids
- *Aloe vera* gel contains mainly polysaccharides, a group of poorly characterized and relatively large molecules
  - Polysaccharides may be qualified as a whole class, but not individually at the molecular level
  - Differentiation of polysaccharides from *Aloe* and various other botanicals remains challenging
- *Aloe* latex (or whole leaf extract) contain anthraquinone glycosides, aloin A (barbaloin) and aloin B (isobarbaloin), with laxative effects
  - Also contain other classes of not well characterized molecules
USP 38-NF22 Monograph for Aloe (1)

• Definition
  – “Aloe is the dried latex of the leaves of Aloe vera (L.) Burm. f. (syn. Aloe barbadensis Mil.), known in commerce as aloe vera, Curaçao aloe, or Barbados aloe; or of Aloe ferox Mill., or of hybrids of Aloe ferox Mill. with Aloe africana Mill. and Aloe spicata L.f., known in commerce as cape aloe (Fam. Liliaceae). Aloe vera contains NLT 16.0% of aloin, and cape aloe and its hybrids contain NLT 6.0% of aloin, both calculated on the dried basis.”

• Identification and Assay: based on the amount of aloin present
  – Aloin is only found in the latex, or outer leaf/rind, of the aloe leaf
  – Polysaccharides, the major portion of Aloe leaf is not tested
USP 38-NF22 Monograph for Aloe (2)

- The USP monograph is **not sufficient** to ensure the quality of the nominated substance, Aloe vera freeze-dried 200:1
  - Chemical characterization of only a small portion (e.g., anthroquinones) of a complex Aloe vera mixture is **not sufficient** to ensure quality and consistency
  - **Aloe vera freeze-dried 200:1** derived from the gel (rather than the latex/skin of Aloe leaf) likely **contains no aloin** (or only trace amounts of anthroquinones).
Quality Considerations

• Aloe vera gel/latex/extracts contain multiple classes of molecules (e.g., polysaccharides, anthraquinones) with complex physicochemical characteristics, and are **poorly characterized**
  – Available analytical methods **could not adequately characterize** and differentiate one Aloe vera product from another
    • Contamination from other botanicals (such as other Aloe species) is difficult to detect
    – Other mechanisms, such as good agricultural and collection practices (GACP), raw material and manufacturing process controls, are necessary

• The nominated substance, Aloe vera freeze-dried (200:1), **is complex and not well defined**
  – The USP Aloe vera monograph only assayed the anthraquinone (e.g., aloin) portion, but not other components (including the major components, polysaccharides)

• In conclusion, we **do not** consider Aloe vera (gel) freeze-dried 200:1 as well-characterized
  – Aloe vera cannot be adequately controlled for compounding drug use from a quality perspective
Aloe vera — Nonclinical Assessment (1)

• Pharmacology
  – Aloe vera products have been reported to possess a wide range of pharmacological activities; however, most claims are not supported by robust data obtained from well-controlled studies
  – There are inconsistent or contradictory nonclinical data regarding wound healing benefits, which might be due to differences in test material and animal models used

• Repeat dose toxicity
  – Repeat oral doses administered via drinking water or diet to mice and rats caused diarrhea, decrease in weight gain, reduction in RBC count, and sperm damage
  – There is a lack of nonclinical data to evaluate the chronic dermal toxicity of Aloe vera
Aloe vera — Nonclinical Assessment (2)

• Mutagenicity
  – Negative in the Ames test for Aloe vera gel, Aloe vera whole leaf extract, and Aloe vera charcoal filtered whole leaf extract
  – Some anthraquinones (e.g., emodin and aloe-emodin) extracted from Aloe vera exhibited genotoxicity in vitro genotoxicity assays

• Developmental and reproductive toxicity
  – Aloe vera has abortifacient activity when taken orally
  – Aloe vera extract induced skeletal malformations in an oral embryofetal toxicity study in rats
Aloe vera – Nonclinical Assessment (3)

• Carcinogenicity
  – In a 1-year photocarcinogenicity study in hairless mice, Aloe gel, aloe-emodin, Aloe whole leaf extract and decolorized leaf extract had a weak enhancing effect on the photocarcinogenic activity of simulated solar light
  – In 2-year oral (drinking water) carcinogenicity studies in mice and rats, Aloe vera whole-leaf extract is an intestinal irritant in both rats and mice and a carcinogen of the large intestine in rats
  – There is a lack of nonclinical data to evaluate the dermal carcinogenicity potential of Aloe vera
Aloe vera — Human Safety Data

- Very limited safety information from clinical trials
  - There is no human safety data to adequately evaluate the safety of the nominated substance, Aloe vera freeze-dried 200:1.
- No pharmacokinetic information available for Aloe vera
- No FAERS or CAERS data specifically for the nominated product
- Aloe vera gel contaminated with other Aloe vera components (e.g., anthraquinones) remains as a potential safety concern for topical applications on open wounds
- Regarding oral use of Aloe vera extracts in laxatives, in 2002 the FDA required that all OTC aloe-containing laxative products be removed from the U.S. market or reformulated because the companies that manufactured them did not provide the necessary safety data (mutagenicity, genotoxicity, and carcinogenicity)
Aloe vera — Human Clinical Safety

• Alternative approved products may be as safe or safer
• Lack of long term dermal safety data and pharmacokinetic data which are necessary for full safety evaluation of topical products
• The safety profile of Aloe vera shows that the anthraquinone derivative in Aloe latex may be unsafe, especially when used at high doses for repeated use (e.g., concerns about potential carcinogenicity)
• There is limited information specifically on the safety of 200:1 freeze dried Aloe products for topical use
Anecdotal reports of efficacy for various indications

- 2012 Cochrane Review on “Aloe vera for treating acute and chronic wounds”
- Comprehensive review of “surgical wounds, burns, lacerations and other skin injuries resulting from trauma.” Chronic wound was defined as any one of the following: “skin ulcers, infected wounds, surgical wounds healing by secondary intention, pressure ulcers, arterial and venous ulcers.”
- Of “178 possibly relevant studies,” only 7 were randomized, controlled studies and therefore deemed adequate for review. The examined literature included various formulations of Aloe vera products, including gels, creams, dressing and mucilage. Apparently, none were for compounded products that specifically included the Aloe vera freeze dried 200:1 nominated product.
Aloe vera — Efficacy

- 2012 Cochrane Review conclusion: “There is currently an absence of high quality clinical trial evidence to support the use of Aloe vera topical agents or Aloe vera dressings as treatments for acute and chronic wounds.”
- 2006 review by Maenthaisong et al., (371 subjects across four clinical trials) also concluded “there is paucity to draw a specific conclusion regarding the effect of Aloe vera for burn wound healing.”
Aloe vera — Historical Use

• Various forms of *Aloe vera*, botanical raw material, used since antiquity
  – Uses: herbal medicine, general tonic, food
  – Medicinal uses
    • Abdominal pain, swelling, burns, skin diseases, urinary disorders, fever, gastritis, constipation, headache, bloodshot eyes, convulsions, hemorrhoids, parasites
• There is insufficient information regarding the historical use of Aloe vera in pharmacy compounding
Aloe vera

- Not well characterized in its physical and chemical properties (especially the major components, polysaccharides)
- Endogenous compound; topical use associated with minor and infrequent side effects
- There is insufficient and conflicting information from controlled clinical trials regarding efficacy of the Aloe vera topical products in the topical treatment of cuts, burns, and wounds. Furthermore, it is not clear whether the products used in those trials contained 200:1 freeze dried Aloe vera
- Various forms of the botanical raw material, Aloe vera, have been used for centuries, but there is insufficient information regarding its historical use in pharmacy compounding
Conclusion

We do not recommend that Aloe vera (freeze dried 200:1) for topical use be placed on the list of bulk substances that can be used for compounding under section 503A of the Federal Food, Drug, and Cosmetic Act.
D-Ribose for Heart Disease

Pharmacy Compounding Advisory Committee Meeting
March 8, 2016

Shari L. Targum, MD, MPH, Clinical Team Leader
Division of Cardiovascular and Renal Products (DCRP)
Review Team

Nancy Xu, MD, Medical Officer
Shari L. Targum, MD, MPH, Clinical Team Leader
Philip Gatti, PhD, Pharmacology/Toxicology Reviewer
Thomas Papoian, PhD, Pharmacology Team Leader
Sreedharan Sabarinath, PhD, Clinical Pharmacology Reviewer
Raj Madabushi, PhD, Clinical Pharmacology Team Leader
Mohan Sapru, PhD, Chemistry, Manufacturing, and Controls Lead
D-Ribose: Background

• Nominated for use in the treatment of “heart disease” and “chronic fatigue syndrome”
• This presentation will focus on the treatment of “heart disease”
• D-ribose has been studied as “adjunct metabolic agent” – not an alternative to the approved therapies for cardiovascular disease
Historical Use

• 1946: Earliest evidence of academic investigator studies in humans
• 1999: Earliest use as dietary ingredient
• Unable to find evidence of pharmacy compounding for drug use
Chemistry

- Monosaccharide with aldehyde ribose functional group at one end
- Naturally occurring compound and component of ribonucleotides and ATP
- Commercially available, and some use it as a food additive or supplement
Quality

• Several synthesis methods, e.g., chemical and enzymatic hydrolysis of yeast RNA to the chemical synthesis of D-ribose from D-arabinose, D-glucose, L-glutamic acid and D-xylose

• Most likely route for synthesis is fermentation-based synthesis

• D-ribose appears to be well characterized physically and chemically
Nonclinical Safety

1) 13-week repeat-dose Wistar rat study (Griffiths 2007): Oral D-ribose added to diet at concentrations of 0, 5, 10 and 20%. Dose-related increase in water consumption, decrease in body weight and increase in cecal weight. No plasma glucose reported.

2) 28-day rabbit study (Bani Ismail 2012): Intravenous D-ribose 420mg/kg. Increase in neutrophil percentage and decrease in plasma glucose levels in males (no values provided).

3) 30-day intraperitoneal administration of D-ribose (0.2 or 2 g/kg) in mice (Han 2011): Compared to glucose control, mice exhibited impairment of spatial learning and memory ability as tested in the Morris water maze.
D-Ribose Human Safety Data

• Limited safety data — no long-term information

• Reports from publications: Hypoglycemia, hyperperistalsis/loose stool/diarrhea (at higher doses), gastrointestinal discomfort, nausea, uric acid elevations (Seifert 2008, Omran 2003, Pliml 1992, and Sawada 2009)

• At 60 g/day — elevations in liver enzymes (2 patients) and increased serum uric acid (3 patients) (Pliml 1992)
Hypoglycemia

• “Asymptomatic mild hypoglycemia” reported in crossover study of 19 healthy subjects receiving oral D-ribose 10 g twice daily for 14 days (Seifert 2008)
• No report of signs/symptoms of hypoglycemia (e.g., sweating, tachycardia, loss of consciousness, seizures)
• Small controlled clinical efficacy studies either excluded diabetics (Omran 2003, Sawada 2009) or did not report effects
• D-ribose may not register on a glucometer, creating potential challenges for optimal insulin management in diabetics
Advanced Glycation End Products (AGEs)

- Nonenzymatic glycation of free amino acid groups by reducing saccharides such as D-glucose and D-ribose
- Associated with vascular and neurologic complications (Nenna 2015)
  - Induce inflammation and intracellular reactive oxygen species
  - AGEs bind to a “cell surface receptor … leading to cross-linking of proteins, accelerated atherosclerosis, glomerular dysfunction, endothelial dysfunction, and altered extracellular matrix composition.” (Harrison’s Principles of Internal Medicine, 19th edition)

Advanced Glycation End Products (2)

- D-ribose is “highly active” in protein glycation, resulting in the production of advanced glycation end products (Han 2014)
- D-ribose injection in mice impaired spatial learning and memory (Han 2011, 2014)
- Many diabetics develop progressive cognitive impairment, and high levels of urinary D-ribose have been measured in diabetic patients. One proposed mechanism for diabetic cognitive impairment has been accumulation of AGEs as a result of high D-ribose concentrations (Han 2014)
- No clinical data concerning the short-term or long-term cognitive effects of D-ribose

D-Ribose Efficacy: Placebo-Controlled Studies

- Pliml (1992): Single-center, open-label, 5 day course of placebo or oral D-ribose 15 g four times daily in patients with stable coronary artery disease:
  - Greater mean treadmill walking time until 1 mm ST depression with D-ribose vs. placebo (276 vs. 223 seconds, respectively, p=0.002), but unblinded ECG readers and no difference in time to angina

- Except Pliml (1992), efficacy publications co-authored by J St. Cyr (Bioenergy, Inc.)
D-Ribose Efficacy: Placebo-controlled studies (2)

- Omran (2003): Single-center double-blind crossover study of placebo or oral D-ribose 5 mg three times daily for 3 weeks in 15 patients with coronary artery disease and congestive heart failure. Quality of life and function improvement in both groups (did not compare between-group differences)

- Sawada et. al. (2009): Randomized, double-blind crossover study in 26 patients with ischemic cardiomyopathy given intravenous placebo or D-ribose 180 mg/kg/hr for 4.5 hours during dobutamine stress testing: No effect on stress-induced ischemia
D-Ribose Efficacy: Uncontrolled Studies

• Vijay (2006): 16 heart failure patients underwent submaximal cardiopulmonary testing at baseline and following oral D-ribose 5 mg three times daily for 8 weeks: Improvement in ventilatory parameters compared to baseline. No mention of effect on functional class, symptoms, distance

• Perkowski (2006): 40 patients received preoperative oral D-ribose before off-pump coronary artery revascularization with improvement in mean cardiac index; no other changes reported
Many Available Therapies for the Treatment of Angina and Congestive Heart Failure

• Approved pharmacologic therapies for angina: calcium channel-blockers, beta-blockers, nitrates, and ranolazine
  – Also non-pharmacologic options: angioplasty, stent placement, coronary artery bypass grafting
• Approved pharmacologic therapies for congestive heart failure: ivabradine, sacubitril/valsartan, beta-blockers (metoprolol, carvedilol), ACE inhibitors or angiotensin receptor-blockers, diuretics, nitrates/hydralazine, digitalis, furosemide
Conclusions

- D-Ribose is well-characterized physically and chemically
- No convincing evidence of meaningful clinical benefit
- Many safe and effective FDA-approved therapies available for angina and congestive heart failure
- Limited safety information: Reports of asymptomatic glucose lowering/hypoglycemia, diarrhea/ hyperperistalsis/loose stool, gastrointestinal discomfort, nausea
- Although used since 1999 as dietary ingredient, there is insufficient information regarding the historical use of pharmacy compounding for drug use.
Conclusions (2)

- Nonclinical data indicate that D-ribose causes non-enzymatic protein glycation, leading to the formation of advanced glycation end products (AGEs).
- In one mouse study, D-ribose administration led to impaired spatial learning and memory ability.
- There are no direct human data that address whether D-ribose affects cognitive ability/memory, although the presence of both cognitive impairment and high urinary levels of D-ribose in diabetic patients raise that possibility.
Recommendation

We do not recommend that D-ribose be included on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act.
D-Ribose for Chronic Fatigue Syndrome

Pharmacy Compounding
Advisory Committee Meeting
March 8, 2016

Janet Maynard, MD, MHS, Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
D-Ribose

Review Team

Janet Maynard, MD, MHS, Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
D-Ribose: Uses Evaluated

• Nominated for use in “heart disease” and “chronic fatigue syndrome”
• This clinical review will focus on use in chronic fatigue syndrome
  – Term chronic fatigue syndrome will be used because this was the term used in the nomination
  – FDA does not recognize a particular definition or name as appropriate for use in clinical trials of drug products for chronic fatigue syndrome, which is also referred to as myalgic encephalomyelitis and systemic exertion intolerance disease
Clinical Assessment: Published Literature

- Open-label uncontrolled pilot study performed to evaluate the use of D-ribose in 41 patients with fibromyalgia and chronic fatigue syndrome (Teitelbaum 2006)
  - Patients received 5 grams of D-ribose 3 times per day until the 280 gram container was empty
  - 5 patients excluded from the analyses due to noncompliance. Thus, 36 patients were included in the analysis
    - Average age: 48 years
    - Previous diagnosis of fibromyalgia: 75%
    - Previous diagnosis of chronic fatigue syndrome: 58%
    - Average duration of therapy: 28 days (17-35 days)
Clinical Assessment: Safety

• Open-label uncontrolled pilot study performed to evaluate the use of D-ribose in 41 patients with fibromyalgia and chronic fatigue syndrome (Teitelbaum 2006)
  – 5 patients that did not complete the study, three discontinued due to adverse events including “hyperanxious feeling (one patient), lightheadedness (one patient), and increased appetite (one patient).”
  – 2 patients did not begin the study
  – Of the remaining 36 patients who completed the study, one patient experienced transient nausea and the other felt mild anxiety. Both of these reactions resolved by lowering the dose of D-ribose

• Division of Cardiovascular and Renal Products (DCRP) provided additional discussion of safety, including hypoglycemia
Clinical Assessment: Efficacy (1)

Table 2. Pre- and Postribose Assessments: All Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>Pre mean (std)</th>
<th>Post mean (std)</th>
<th>Difference (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy level</td>
<td>36</td>
<td>3.8 (1.1)</td>
<td>5.5 (1.5)</td>
<td>1.7 (1.1, 2.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep</td>
<td>36</td>
<td>4.8 (1.6)</td>
<td>6.0 (1.9)</td>
<td>1.2 (0.6, 1.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mental clarity</td>
<td>36</td>
<td>4.9 (1.5)</td>
<td>5.7 (1.7)</td>
<td>0.8 (0.3, 1.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Pain</td>
<td>36</td>
<td>4.9 (2.3)</td>
<td>5.6 (2.2)</td>
<td>0.7 (0.1, 1.3)</td>
<td>0.026</td>
</tr>
<tr>
<td>Well-being</td>
<td>36</td>
<td>4.3 (1.3)</td>
<td>5.6 (1.5)</td>
<td>1.3 (0.8, 1.9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI, confidence interval.

Clinical Assessment: Efficacy (2)

### Table 3. Pre- and Postribose Assessments per Diagnosis

<table>
<thead>
<tr>
<th>Category</th>
<th>FMS (N = 15)</th>
<th>CFS (N = 9)</th>
<th>Both FMS/CFS (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre mean (std)</td>
<td>Post mean (std)</td>
<td>Improvement (%)</td>
</tr>
<tr>
<td>Energy</td>
<td>3.7 (1.0)</td>
<td>5.5 (1.5)</td>
<td>1.8 (48%)</td>
</tr>
<tr>
<td>Sleep</td>
<td>4.4 (1.2)</td>
<td>5.9 (1.6)</td>
<td>1.5 (34%)</td>
</tr>
<tr>
<td>Mental clarity</td>
<td>4.7 (1.0)</td>
<td>5.7 (1.8)</td>
<td>1.0 (21%)</td>
</tr>
<tr>
<td>Pain</td>
<td>4.5 (2.3)</td>
<td>5.5 (2.0)</td>
<td>1.0 (22%)</td>
</tr>
<tr>
<td>Well-being</td>
<td>4.1 (1.0)</td>
<td>5.7 (1.5)</td>
<td>1.6 (39%)</td>
</tr>
</tbody>
</table>

FMS, fibromyalgia; CFS, chronic fatigue syndrome.

Clinical Assessment: Efficacy (3)

- Limited conclusions are possible from the available data. The single study identified was open label. Thus, it did not have a comparator group. Further, the number of patients with chronic fatigue syndrome was small and the clinical interpretation of the numerical changes is unclear.
Clinical Assessment: Efficacy (4)

• This review focused on the intended use for chronic fatigue syndrome, which is a serious disease. No treatments have been approved by FDA for chronic fatigue syndrome.

Conclusion
While the efficacy of D-ribose for chronic fatigue syndrome is unclear, it is used by some patients for treatment of symptoms associated with chronic fatigue syndrome.
General Conclusions

• As discussed by DCRP, D-ribose appears well characterized physically and chemically
• Refer to DCRP regarding historical use in compounding
• Limited safety data from one uncontrolled study suggest D-ribose is generally well-tolerated in chronic fatigue syndrome
• Other safety considerations have been reviewed by DCRP
• While the efficacy of D-ribose for chronic fatigue syndrome is unclear, it is used by some patients for treatment of the symptoms associated with chronic fatigue syndrome
• There are no approved agents indicated for the treatment of chronic fatigue syndrome, a serious disease
Recommendation

We recommend that D-ribose be placed on the list of bulk drug substances that can be used in compounding under section 503A of the Federal, Food, Drug, and Cosmetic Act for the proposed indication of chronic fatigue syndrome.
D-Ribose

Pharmacy Compounding
Advisory Committee Meeting
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Charles J. Ganley, MD
Director, Office of Drug Evaluation IV
Office of New Drugs (OND)

- Office of New Drugs
- Within OND, there are six sub-offices and within each sub-office there are divisions
  - Office of Drug Evaluation I  [Cardiovascular-Renal, Neurology, Psychiatry]
  - Office of Drug Evaluation II  [Metabolism-Endocrinology, Pulmonary-Allergy-Rheumatology, Anesthesia-Analgesia-Addiction]
  - Office of Drug Evaluation III  [Dental-Dermatology, Gastroenterology-Inborn Errors, Bone-Reproductive-Urologic]
  - Office of Drug Evaluation IV  [Medical Imaging, Nonprescription Drug, Pediatric-Maternal Health]
  - Office of Antimicrobial Products  [Anti-infective, Antiviral, Transplant-Ophthalmology]
  - Office of Hematology and Oncology Products  [Oncology 1, Oncology 2, Hematology, Hematology Oncology Toxicology]
Division Recommendations

- The recommendation of each division is based on the division’s benefit-risk assessment for the uses being considered under the purview of the division’s therapeutic expertise.
- For D-Ribose, reviews by DPARP, DCRP, and DMEP of information specific to each therapeutic use resulted in disparate recommendations.
- The recommendations for each use, as explained in the reviews and presentations, and the rationale for the recommendations are clear.
ODEIV Review

• ODEIV was assigned to review the information in each division memorandum and making an overall recommendation with the concurrence of the Director of the Office of New Drugs.

• This recommendation will represent the position of the FDA on this nomination.

• The OND memo provides the rationale for the overall recommendation.
D-Ribose Nomination

- There are numerous websites that advocate the use of D-Ribose for a variety of conditions.
- Nominated for heart disease
- Nominated for chronic fatigue syndrome [Myalgic Encephalomyelitis /Chronic Fatigue Syndrome (ME/CFS)]
Current Availability of D-Ribose

- D-Ribose has been marketed as a dietary ingredient
- It is sold as a powder, tablets and capsules, either alone or in combination with other dietary ingredients
- It can be purchased today without a prescription on the internet or in stores
- We were unable to find information on the compounding of D-Ribose
D-Ribose as a Food Additive

- FDA received a Generally Recognized as Safe (GRAS) notice for D-ribose from Bioenergy, Inc. on February 8, 2008
- The notice informed FDA of Bioenergy's view that D-ribose is GRAS provided it is used in conjunction with an additional carbohydrate energy source.
- November 10, 2008 FDA letter acknowledges that:
  - FDA has no questions at the time regarding Bioenergy’s conclusion
  - Bioenergy concluded that D-ribose is GRAS
  - FDA has not made its own determination
  - Bioenergy has the continuing responsibility to ensure that food ingredients that they market are safe.
OND Assessment of D-Ribose

- Randomized clinical trials conducted for evaluation in cardiovascular disease did not establish a benefit.
- A single study conducted in patients with ME/CFS and/or fibromyalgia does not provide evidence of effectiveness because of significant design limitations.
- D-ribose is associated with dose related asymptomatic hypoglycemia.
- D-ribose can bind with proteins to form Advanced Glycation Endproducts (AGEs).
D-Ribose Study in Fibromyalgia/[ME/CFS]

- Subjects enrolled through Vitality 101 website (Investigator’s) in response to emailed newsletter to patients
- Not clear how subjects were screened for fibromyalgia or ME/CFS
- Sent questionnaires and 280 gram container of D-ribose (Corvalen); instructed to ingest 5 grams three times/day until finished
- Not blinded, not controlled; 9 subjects had ME/CFS
- Questionnaire completed at start and completion
- Visual Analogue Scale (1 – 10) questions for energy, sleep, mental clarity, pain and sense of well being
- 36 of 41 completed; no significant benefit in ME/CFS subjects
Advanced Glycation Endproducts (AGEs)
Ribose and AGEs

• Ribose glycation occurs more readily than glucose glycation
• Ribose protein glycation occurs in animals administered d-ribose
• Ribose protein glycation demonstrated in vitro in human bone
• In diabetics, glucose macromolecule glycation leads to injury in tissues (retinopathy, nephropathy, atherosclerosis.)
• With chronic use of d-ribose, what is the consequence of ribose glycation in tissue?
OND Recommendation for D-Ribose

• Office of New Drugs does **not recommend** D-Ribose for the 503A bulks list because:
  • No history of compounding as a drug
  • No evidence to support the effectiveness for the conditions nominated
  • Potential safety concerns with large amounts (hypoglycemia) and for extended period of time (AGEs)
D-Ribose is a Dietary Ingredient

- D-Ribose is marketed as a dietary ingredient/will remain available
- Patients with ME/CFS will still be able to obtain D-ribose if they choose to take this ingredient
ME/CFS

- D-ribose has not been adequately studied in ME/CFS
- ME/CFS is a serious, chronic, complex, systemic disease that often can profoundly affect the lives of patients
- Over the past several years, there have been efforts by the FDA, NIH, HHS and the Institute of Medicine to enhance the understanding of the disease
- Open label, uncontrolled studies with D-ribose in patients with this disease do not answer the important effectiveness questions
Resources for Information on ME/CFS

- [http://www.fda.gov/Drugs/NewsEvents/ucm319188.htm](http://www.fda.gov/Drugs/NewsEvents/ucm319188.htm)
Chondroitin Sulfate

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Javier Muniz, MD
CDR, United States Public Health Service
Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Review Team

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BeLinda Hayes, PhD, Pharmacology/Toxicology Reviewer, DAAAP
John Feeney, Clinical Team Leader, DAAAP
R. Daniel Mellon, PhD, Pharmacology/Toxicology Supervisor, DAAAP
Norman Schmuff, PhD, Associate Director for Product Quality, Office of Pharmaceutical Quality
Chondroitin Sulfate: Uses Evaluated

- Nominated for topical use for the treatment of joint pain associated with osteoarthritis (OA)
Chemistry (1)

- Polymer composed of alternating N-acetylgalactosamine and glucuronic acid

![Chemical structure of polymer](image)

- Remarkably stable under neutral conditions at low temperature
- Degradation and desulfation at elevated temperatures
- Breakdown of polysaccharide linkages observed under acidic and basic conditions
Chemistry (2)

• Commercially available products are unspecified mixtures with mainly two major components
  – Chondroitin sulfate A or chondroitin 4-sulfate
  – Chondroitin sulfate C or chondroitin 6-sulfate

• Usually a white powder, available as sodium salt

• Soluble in water

• Residual proteins from animal tissues may introduce problems
  – BSE import alert
Nonclinical (1)

- **Pharmacology**
  - Chondroitin sulfate (CS) is the most abundant glycosaminoglycan (GAG) in the connective tissue including articular cartilage. Chondroitin sulfate is essential for the structural and functional integrity of cartilage since it is the majority constituent of GAG. It provides much of the cartilage tissue resistance to compression.

- **Animal models of joint damage suggest some benefits when administered orally or injected into the knee joint**
  - No clear mechanism of action
  - Hypotheses primarily based on in vitro studies w/ high concentrations of CS:
    - Anti-apoptotic effect on chondrocytes?
    - Increase synthesis of proteoglycans? (Provides building blocks?)
    - Reduces protease function? (Reduced joint degradation?)
    - Anti-inflammatory properties?
    - Alterations in sub-chondral bone?
Nonclinical (2)

- **Pharmacokinetics**
  - No topical data – expect minimal if any absorption
  - Oral administration: low oral bioavailability, likely absorption of metabolic byproducts of CS

- **Safety pharmacology**
  - No topical studies
  - Extremely limited data with parenteral route of administration.
  - No evidence of adverse effects on cardiovascular, gastrointestinal, or renal systems. No data on central nervous system or respiratory system

- **Toxicology**
  - No topical toxicology studies
  - No oral toxicology studies testing CS
Nonclinical (3)

- **Mutagenicity**
  - Not genotoxic in-vitro

- **Developmental and reproductive toxicity**
  - Subcutaneous injection study in mice: Reports potential adverse effects
    - Cleft palate
    - Flexed/curling tails
    - Growth inhibition of fetus
  - No adverse effects reported following oral administration in rats or mice
  - The actual study reports are not available, limited utility for topical

- **Carcinogenicity**
  - No studies, dermal or oral
Nonclinical (4)

- Nonclinical conclusions:
  - Nonclinical safety profile not adequately characterized
  - No evidence of adverse effects based on limited data available

- BUT, there are data missing:
  - Chronic toxicology in two species
  - Reproductive and development toxicology
    - Fertility and early embryonic development
    - Embryo-fetal development two species
    - Pre- and postnatal development

- Carcinogenicity assessment in two species

- Dermal toxicology safety assessment (general toxicity, photo safety, dermal carcinogenicity, hypersensitivity testing)
Clinical Safety (1)

- Literature reports
  - Topical chondroitin as part of a combination product (chondroitin, glucosamine, camphor, peppermint oil) was well-tolerated for two months in about 30 patients treated for OA knee pain (Cohen et al. 2003)
  - Extensive experience with oral chondroitin
    - Notable AEs include: Allergic reactions, elevated liver enzymes, and drug-drug interactions
    - Cases of international normalized ratio (INR) elevation with concomitant warfarin

- FAERS and CAERS databases
  - Minimal experience with topical chondroitin
  - One case of rash with topical chondroitin had multiple confounders
  - Cases of INR elevation with concomitant warfarin
Clinical Safety (2)

• Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)
  – Oral route of administration
  – 24 week treatment period, with a 2-year extension
  – 318 patients assigned to chondroitin-only and 317 patients to chondroitin/glucosamine
  – No serious adverse events (SAEs) with chondroitin monotherapy attributable to drug

• Summary of product characteristics (SPC) for Droglican (oral chondroitin product approved in Europe) lists the following undesirable effects:
  – Gastrointestinal disorders, nausea (rare); hypersensitivity (very rare); edema, fluid retention (very rare)
  – Special Warnings and Precautions states that patients with impaired glucose tolerance should be monitored and that “in very rare occasions (< 1/10,000) in such patients … cases of edema and/or water retention [have been reported]
Clinical Safety (3)

• No dose-response information orally or topically
• Clinical safety conclusions
  – Minimal experience reported with topical chondroitin
  – One FAERS case of rash with topical chondroitin had multiple confounding factors
  – Extensive experience with oral chondroitin has been summarized
  – There may be an interaction with warfarin and a risk for bleeding associated with the oral use of chondroitin, based on cases of drug-drug interaction in both FAERS and the literature. None of the warfarin interaction cases were specifically linked to topical use of chondroitin
Clinical Efficacy (1)

• Cohen et al. (2003) studied the effects of a topical cream containing chondroitin, glucosamine, camphor, and peppermint oil
  – Randomized (R), placebo-controlled (PC) parallel-group trial, n=63
  – Two-month treatment period
  – Patients were instructed to apply the creams generously to painful joints and repeat as necessary
    • Average number of applications per day was about three
  – Improved pain scores observed at 8 weeks
  – A combination product was used in the study The study was not designed to investigate the efficacy of the individual components
  – Concerns raised about adequacy of the blind
    • Texture differences between the placebo and active creams
Clinical Efficacy (2)

• Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)
  – R, PC and active-controlled (celecoxib) trial investigating the efficacy of oral glucosamine and oral chondroitin sulfate, n=1583
  – Six-month treatment period
  – Full factorial design; placebo and following four treatment groups
    • 1200 mg of oral chondroitin sulfate daily
    • 1500 mg of oral glucosamine hydrochloride daily
    • Both chondroitin and glucosamine
    • 200 mg of celecoxib daily
  – Chondroitin, alone or in combination with glucosamine, was not effective in increasing the responder rate
  – A sub-group analysis was performed including only patients with baseline pain severity of 301 or greater on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale
Clinical Efficacy (3)

GAIT Overall Results:

<table>
<thead>
<tr>
<th></th>
<th>Chondroitin</th>
<th>Glucosamine</th>
<th>Combination</th>
<th>Placebo</th>
<th>Celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Responders (percent)</td>
<td>208/318 (65)</td>
<td>203/317 (64)</td>
<td>211/317 (67)</td>
<td>188/313 (60)</td>
<td>223/318 (70)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.17</td>
<td>0.30</td>
<td>0.09</td>
<td></td>
<td>0.008</td>
</tr>
</tbody>
</table>

GAIT Sub-Group Results:

<table>
<thead>
<tr>
<th></th>
<th>Chondroitin</th>
<th>Glucosamine</th>
<th>Combination</th>
<th>Placebo</th>
<th>Celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Responders (percent)</td>
<td>43/70 (61)</td>
<td>46/70 (66)</td>
<td>57/72 (79)</td>
<td>38/70 (54)</td>
<td>50/72 (69)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.39</td>
<td>0.17</td>
<td>0.002</td>
<td></td>
<td>0.06</td>
</tr>
</tbody>
</table>
Clinical Efficacy (4)

• 1995-2005, pre-GAIT publications
  – Busci et al. (1998)
  – Uebelhart et al. (1998)
  – Das et al. (2000)
  – Uebelhart et al. (2004)

• 2006-present, post-GAIT publications
  – Mazieres et al. (2007)
  – Kahan et al. (2009)
  – Moller et al. (2010)
  – Gabay et al. (2011)
  – Zegels et al. (2013)
Historical Use in Compounding

• Historical use
  – No information was found for the historical use of chondroitin in pharmacy compounding, either topically or orally. Oral chondroitin has been discussed in the medical literature dating back to the 1980s

• Medical conditions treated
  – Has been used by multiple routes of administration and for the treatment of multiple conditions, including joint pain with OA, interstitial cystitis, and overactive bladder
  – Used in some products for the treatment of dry eyes and corneal inflammation and for cataract surgical procedures
Conclusions

• Chondroitin sulfate is an unspecified mixture that can be characterized with various analytical techniques and is stable both as a solid and in aqueous solution.
• There are insufficient data to support the safety or efficacy of topical chondroitin in the treatment of joint pain associated with OA.
• A number of safe and effective FDA-approved agents are available for the treatment of joint pain associated with OA.
• The possible use of topical chondroitin is not advisable given the availability of approved products for this indication that have been demonstrated to be safe and effective in well-controlled clinical trials.
• Further clinical investigation with topical chondroitin should be monitored through the IND process.
• There is insufficient information on the extent of use of topical chondroitin in compounding to evaluate the significance of its historical use.
We do not recommend that chondroitin sulfate for topical use be placed on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act.
Acetyl-L-Carnitine

Pharmacy Compounding Advisory Committee Meeting
March 8, 2016

Kenneth Bergmann, MD
Medical Officer, Division of Neurology Products (DNP)
Acetyl-L-Carnitine

Review Team

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Acetyl-L-Carnitine

Nominated uses:
• Peripheral neuropathy
• Cirrhosis of the liver (hepatic encephalopathy)
• Alzheimer’s disease
Chemistry (1)

- Formula: C$_9$H$_{17}$NO$_4$
- Molecular weight: 203.236 g/mol
- Melting point: 145 °C (decomposition observed)
- Solubility: Very soluble in water
- Stability: Stable in solid forms under ordinary storage conditions. Degradation may happen in aqueous solutions.
- Structure characterization: Well characterized
Chemistry (2)

- Possible synthetic route:

\[
\begin{align*}
\text{L-carnitine} & \xrightarrow{\text{reaction}} \text{Acetyl-L-carnitine} \\
\text{Or} & \\
\text{L-carnitine} & \xrightarrow{\text{reaction}} \text{Acetyl-L-carnitine}
\end{align*}
\]

- Likely Impurities: Starting materials (L-carnitine), residual reagents and byproducts

Conclusion: Acetyl-L-carnitine (ALC) is a small organic molecule. It is stable as a solid under ordinary storage conditions, but may have stability issues when formulated as an aqueous solution.
Nonclinical Safety Pharmacology

• Synthesized in human brain, liver, and kidney by acetylation of carnitine
  – Involved in mitochondrial energy homeostasis and in phospholipid and acetylcholine synthesis

• Safety pharmacology
  – Intraperitoneal (IP) administration of 1 mg/kg was associated with increased activity and rearing behavior in male Sprague-Dawley rats
  – No reports of cardiac or respiratory effects
Nonclinical Safety Toxicology (1)

- **Acute toxicity**
  - IV administration in mice was associated with clonic convulsions, cyanosis, and death ($\text{LD}_{50} = 1420 \text{ mg/kg}$)
  - No adverse effects were associated with IP administration of 300 mg/kg in rats

- **Repeat dose toxicity**
  - No adverse effects were associated with oral administration in mice (406 mg/kg for 4 weeks), rats (300 mg/kg for 2 weeks), or dogs (28 mg/kg for 133 days)
  - No adverse effects were associated with IP administration in rats (250 mg/kg for 5 days) or intramuscular injection in monkeys (50 mg/kg for 2 weeks)
Nonclinical Safety Toxicology (2)

• Developmental and reproductive toxicity
  – Dietary administration over 3 reproductive cycles did not affect litter size or offspring weight in rats
• No mutagenicity, carcinogenicity, or toxicokinetic data were available

Conclusion: Available non-clinical information is limited, but did not reveal any significant toxicity associated with acetyl-L-carnitine administration in animals.
Clinical Pharmacology

- L-Carnitine (parent molecule) synthesized from dietary proteins and metabolized to ALC
- Dietary bioavailability 54-87%
- Stereospecific transport results in up to 100-fold increase in intracellular concentration
- All L-carnitine related compounds exist in a concentration-based dynamic intracellular balance (see next slide)
- Mostly excreted in urine (unabsorbed dietary carnitine is broken down in large intestine by GI bacteria)
- Excretion (return to baseline after IV single dose)
  - Carnitine 24 h
  - Acetyl-L-Carnitine 12 h

Rebouche. Ann NY Acad Sci 2004, 1033:30-41
The Carnitine Pool

Clinical Safety (1)

Sources of information

• L-Carnitine label (Carnitor™ NDA 018948, Sigma Tau)

• CDER’s Office of Surveillance and Epidemiology: FDA Adverse Events Reporting System (FAERS) – voluntary reporting by patients and healthcare providers for serious adverse events for prescription drugs (e.g.: death, life-threatening, hospitalization, disability, congenital anomaly, etc.). ALC would only appear if it were co-administered.

• Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS) – voluntary reporting by consumers of side effects of dietary supplements. Reports include scant information about the individual’s baseline medical condition, how much drug was taken, the seriousness of the event, and whether recovery occurred.

• Clinical trials that include safety reporting.
Clinical Safety (2)

L-Carnitine label (Carnitor NDA 018948, Sigma Tau)

• No known contraindications or warnings
• No reports of L-carnitine overdose
• Has not been fully evaluated in patients with renal insufficiency. Chronic administration of high doses in patients with renal insufficiency may result in accumulation of the potentially toxic metabolites (trimethylamine and trimethylamine-N-oxide)
• Drug interaction: Warfarin - reports of international normalized ratio (INR) increase
• The effect on human pregnancy and unborn fetus are not known. Likely to be excreted in human milk
• Common: Transient nausea and vomiting, dizziness
• Less frequent: Body odor and gastritis
• Seizures have been reported to occur in patients, with or without pre-existing seizure activity. In patients with pre-existing seizure activity, an increase in seizure frequency and/or severity has been reported

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018948s026,019257s012,020182s013lbl.pdf
Clinical Safety (3)

  - 13 cases (5 for peripheral neuropathy, 8 not reported)
  - Attribution to ALC could not be determined, or it was unlikely given the limited case details, or the presence of a more likely alternative etiology
  - All cases reported at least one additional suspect product

  - Broad search terms: Events reported with products containing any form of carnitine
  - Reports: ALC was the solitary ingredient in only 8 events of 68 identified
  - Products in the other reports contained ALC formulated with a variety of vitamins, minerals, trace metals, and unidentifiable proprietary named ingredients
  - Other important health problems co-occurred in 31 patients. Of interest: convulsions (5), gastrointestinal distress (7), and allergic complaints (7), e.g., rash, swelling of face, hypersensitivity, etc.
Clinical Safety (4)

Clinical trials that include safety reporting

• No new or previously undescribed adverse drug related reactions were described when compared to L-carnitine

• The most common adverse drug reactions collected in a non-systematic fashion from case reports and trials:

  • Gastrointestinal distress
  • Hypertension
  • Headache
  • Dizziness
  • Fever,
  • Vomiting
  • Paresthesia,
  • Cough

  • Tachycardia
  • Palpitation
  • Peripheral edema
  • Vertigo
  • Rash
  • Bronchitis
  • Gastritis
  • Body odor
Clinical Efficacy (1a)

Peripheral Neuropathy

- Studied for both the prevention and treatment of peripheral neuropathy related to cancer chemotherapy, diabetes mellitus (DM), and human immunodeficiency virus (HIV) treatment
- Small single center trials showed small improvement in nerve conduction velocity or patient reported pain. No measures of the clinical meaningfulness of the outcome (e.g. Bianchi, et al., 2005)
- DeGrandis and Minardi (2002): blinded, randomized, placebo-controlled, multicenter trial in 333 DM neuropathy patients. ALC given 2 grams/day for one year. Small improvement of nerve conduction (still within abnormal range) without clinical benefit
Clinical Efficacy (1b)

Peripheral Neuropathy

• Randomized multicenter trials performed with well-defined methodologies and rigorous controls did not demonstrate efficacy:
  – Treatment of antiretroviral toxic neuropathy in patients with HIV infection (Youle et al., 2007)
  – Prevention of sagopilone-induced peripheral neuropathy (Campone et al., 2013)
  – Prevention of chemotherapy-induced peripheral neuropathy in patients with multiple myeloma (Callander et al., 2014)
  – Prevention of taxane-induced neuropathy in adjuvant breast cancer therapy (Hershman et al., 2013)
Cirrhosis of the liver

- Liver disease causes generalized brain dysfunction known as hepatic encephalopathy (HE). This results, in part, from the inability of the liver to detoxify ammonia in the body. (Ammonia is a metabolic by-product of dietary proteins)

- Diagnosis of HE is made by measuring arterial ammonia, with supportive evidence from electroencephalography and psychometric testing

- Jiang et al., (2013) systematically reviewed the therapeutic efficacy of ALC in patients with hepatic encephalopathy in 33 trials (6 trials were blinded and randomized but these also had irregularities in design, conduct, and analysis)
  - Serum ammonia was reduced on average 26 mg/dl but this was not clinically meaningful
Clinical Efficacy (3a)

Alzheimer’s disease

• Cochrane Collaboration Review (Hudson and Tabet, 2003)
  – 33 randomized, placebo-controlled trials
  – 16 trials assessed as appropriately designed (6 of these were multicenter trials)
  – The test dose of ALC:
    • 2 to 3 gm daily
    • 12 to 52 weeks
    • more than 1,400 patients
  – All trials assessed the potential cognitive effect of ALC on patients with mild to moderate dementia and, in addition, most considered the severity of dementia, functional ability, and clinical global impression
Clinical Efficacy (3b)

Alzheimer’s disease

• Cochrane Collaboration assessment:
  “There is evidence for benefit of ALC on clinical global impression ... and on the [Mini Mental State Exam] at 24 weeks, but there is no evidence using objective assessments in any other area of outcome. Given the large number of comparisons made, the statistically significant results may be due to chance. At present there is no evidence to recommend its routine use in clinical practice.”

• European Food Safety Authority review of ALC:
  “a cause and effect relationship has not been established between the consumption of acetyl-L-carnitine and contribution to normal cognitive function” (EFSA Panel, 2011)
Historical Use in Compounding

• The extent of ALC use in pharmacy compounding is unknown
• ALC has been available since at least 1964. It has been widely available as a dietary ingredient in dietary supplements for at least three decades
• By 1983, it was understood as being a naturally occurring endogenous chemical substance in people as a result of L-carnitine metabolism
• L-carnitine was approved for use in the United States in 1985
U.S.-Approved Therapies

- Peripheral neuropathy: No approved treatments for the prevention of peripheral neuropathy from chemotherapy or diabetes mellitus. FDA-approved medications for pain associated with peripheral neuropathy: Cymbalta (duloxetine), Lyrica, (pregabalin), and Nucynta ER (tapentadol)
- Cirrhosis of the liver: Treatment reduces the hyperammonemia of cirrhosis by targeting absorption from food, production, and elimination: Lactulose and Xifaxan (rifaximin) are the mainstays of current FDA-approved therapy
- Alzheimer’s disease: Aricept (donepezil), Exelon (rivastigmine), Namenda (memantine), and Razadyne (galantamine) are FDA-approved for the treatment of dementia caused by AD
Conclusions

- The physical and chemical properties of ALC are well characterized
- The extent of ALC use in pharmacy compounding is unknown
- The safety profile suggests that it is well tolerated when given orally up to 3 g daily. It must be used with caution in anyone using anticoagulant drugs (e.g., warfarin), persons suffering from seizures, and in persons with renal insufficiency (a major route of elimination)
- Extensive investigation in large, randomized, blinded and placebo-controlled trials fails to support its efficacy for any of the proposed uses
- The disorders included in the nomination are serious medical conditions for which safe and effective treatments are available in the United States
Recommendation

We do not recommend that Acetyl-L-Carnitine be placed on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act.
Introduction to Demonstrably Difficult to Compound Drug Products and Review of Criteria

Pharmacy Compounding Advisory Committee Meeting
March 9, 2016

Cyrus Agarabi, Pharm.D., R.Ph., M.B.A., Ph.D.
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Division of Biotechnology Review and Research II
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Conditions on Difficult to Compound Drug Products

• Section 503A states that the compounded drug product is not one identified by FDA as a drug product that “presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.”

• Section 503B states that the compounded drug, or category of drugs, either is not identified on a list published by the FDA as one that “present[s] demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into the account the risks and benefits to patients,” or is compounded in accordance with “conditions that are necessary to prevent the drug or category of drugs from presenting [such] demonstrable difficulties.”

1. Complex Formulation
2. Complex Drug Delivery Mechanism
3. Complex Dosage Form
4. Bioavailability
5. Compounding Process Complexity
6. Physicochemical or Analytical Testing Complexity
PCAC Feedback on the Proposed Evaluation Criteria

• At the June 2015 meeting, the Committee recommended consideration of:
  – the compatibility and/or stability of the active pharmaceutical ingredients in the final dosage form;
  – the container closure system which may interact with the compounded drug;
  – The toxicity of the drug as it relates to (1) potential harm to the patient or caregiver and (2) potential toxicity due to carryover or cross contamination.
Updates to the Proposed Evaluation Criteria

- We have updated criteria 1 and 3 to incorporate the Committee’s recommendations.
- The handling of hazardous drugs (e.g., toxicity) may be addressed elsewhere, for example:
  - cGMPs for Outsourcing Facilities;
  - USP <800> *Hazardous Drugs—Handling in Healthcare Settings*;
  - Criterion 5 on Compounding Process Complexity (specialized facility and/or equipment).
- We have also revised the document to clarify the description of each factor to more specifically track the statutory language.
Revised Criterion 1: Complex Formulation

Complex formulation refers to a formulation in which the ingredients (active pharmaceutical ingredients (APIs) or excipients) are required to have certain physicochemical characteristics or properties that are necessary to achieve or maintain the proper performance of the drug product. For example, crystalline (including polymorphs) or amorphous forms, or chirality or particle size of an API might be critical in some formulations to the safety and efficacy of the drug product. The compatibility and/or stability (physical and chemical) of the API(s) and/or excipients in the final dosage unit may also be evaluated to determine if the compounded drug product has a complex formulation. A complex formulation may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.
Revised Criterion 3: Complex Dosage Form

Complex dosage form refers to physical dosage units with characteristics that are difficult to consistently achieve or maintain. Complex dosage form also refers to container closure systems that may interact with the compounded drug and affect its intended use, either through physical (inconsistent dose administration) or chemical interactions between the compounded drug and the container closure system. Drug products may have very simple formulations, such as a single API, and a simple delivery mechanism, such as an injection, but the compounded drug product may be complex because the physical properties of the dosage form are difficult to achieve or maintain. Complex dosage forms may include, for example, propellant based aerosolized products or dry powder inhalers. A complex dosage form may present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug product.
Drug Product Being Proposed for the Difficult to Compound List

1. **Metered Dose Inhalers**: Brian Rogers, Chemistry, Manufacturing, and Controls (CMC) Reviewer, DPAII/Office of Process and Facilities/Office of Pharmaceutical Quality

2. **Dry Powder Inhalers**: Craig M. Bertha, CMC Lead, Branch IV/Division of New Drug Products II/Office of New Drug Products/Office of Pharmaceutical Quality
Metered Dose Inhalers (MDIs)

Pharmacy Compounding Advisory Committee Meeting
March 9, 2016

Brian Rogers, PhD (Quality Reviewer)
Division of Process Assessment II
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Metered Dose Inhalers (MDIs)

Review Team

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Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jianmeng Chen, MD, PhD (Clinical Pharmacology Reviewer)
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MDI Background

- Delivers metered aerosol to lungs
  - Oral inhalation
  - Delivers small precise formulation volume (25 – 100 μL)
- Most common uses: treatment of asthma and chronic obstructive pulmonary disease (COPD)
- Other uses:
  - Respiratory infections
  - Cystic fibrosis
  - Systemic drug delivery
MDI Background (2)

- Formulation – Suspension or solution
- Formulation Components
  - Active Pharmaceutical Ingredient (API)
  - Propellant – Major component
  - Co-solvent* (solution) or surfactant (suspension)
- Pressurized system
  - Propellant is liquefied gas
  - Rapid expansion provides energy to create aerosol

* A co-solvent is an excipient which aids in solubilizing or processing one of the formulation components, typically the API
MDI Background (3)

Components

• Container surfaces should be inert to the physically unstable formulation

• Canister
  – Container - sealed by metering valve to contain pressure
  – May contain sufficient formulation for hundreds of individual doses (a dose as prescribed may consist of 1-8 actuations of the device)

• Metering valve
  – Consistently measures precise amount of formulation
  – Seals canister to protect bulk formulation from environment

• Actuator
  – Creates consistent aerosol by rapid evaporation through orifice
  – Orifice needs precise dimensional control to create consistent plume
MDI Background (4)

Design of Typical MDI

- Canister
- Gas phase
- Liquid phase (formulation)
- Retaining cup
- Actuator
- Metering chamber
- Expansion chamber
- High-velocity spray
- Actuator nozzle

Metering Valve

- HOUSING/BODY (Acetal Resin)
- SPRING
- INSIDE GATHERING RING (Polyethylene)
- METERING GASKET
- METERING CHAMBER (Acetal Resin)
- FERRULE (Anodized Aluminum)
- SEALING GASKET
- DIAPHRAGM/STEM GASKET
- STEM (Acetal Resin)
Critical Aspects

- Consistent dosing
  - Ensures safety and efficacy
  - Determines correct site and quantity of API deposition (µg – mg)

- Performance attributes
  - Aerodynamic particle size distribution (APSD)
    - Determines site of deposition in airway
    - Narrow effective range of API particle sizes (< 5 µm)
  - Delivered dose uniformity (DDU)
    - Determines quantity of deposition in airway
    - Affected by manufacturing, formulation, container closure
MDIs Have a Complex Formulation

Components

• Critical API properties that may affect safety and efficacy
  – Particle size distribution – high surface area in MDIs (high surface energy)
  – Particle morphology (e.g., shape and texture) – affects surface area (energy)
  – Polymorphic form (type of crystal structure) – affects physical stability
  – Solubility – Low solubility decreases potential for recrystallization (particle growth)
  – Bulk density – Affects creaming or settling in suspension formulation
  – Moisture or residual solvent content – Presence affects physical stability
  – Purity – No suitable compendial monographs for inhalation grade APIs

• Excipients
  – Propellant – Poor solvent – Control of impurities is critical for safety
  – Co-solvent – Solution formulation – Changes water content, impurities levels
  – Surfactant – Suspension formulation – Improves physical stability
  – No suitable compendial monographs for inhalation grade materials
MDIs Have a Complex Formulation (2)

Suspension Formulation Stability

- Suspension formulations – tight controls needed to maintain stability
- Affected by API properties:
  - Creaming or settling in liquid formulation impacts dose uniformity
  - Adherence to container closure/other formulation particles
  - Ostwald ripening – recrystallization, increases particle size distribution
  - Changing polymorphic form in suspension – creates solubility and stability issues
- Extensive characterization studies necessary with proposed device
  - To detect formulation physical instability/interaction with device
  - To optimize concentration of additives
- Instability may result in subtherapeutic or supratherapeutic dosing
MDIs Have a Complex Formulation (3)

Conclusion

MDIs have a complex formulation that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on safety or effectiveness

• Critical that it promotes delivery of consistent API mass
• Need consistent size droplets or particles from metering valve under all in-use conditions throughout life
• Unique components
  – Need predictable and controllable chemical composition and physical stability
  – Solid formulation components are physically unstable
  – Incorrect formulation will not aerosolize correctly and could deliver too much or too little drug, affecting safety and/or effectiveness of the compounded drug.
**MDIs Have a Complex Drug Delivery Mechanism**

- It is critical that MDIs consistently measure/deliver complex formulation to ensure safety and efficacy
- Drug delivery determines drug product performance and is tied to formulation properties
  - The actuator needs to produce consistent aerosol plume geometry for consistent dose delivery
  - Metering valve
    - Delivers consistent fine APSD (API) for appropriate lung deposition
    - Should be inert to formulation, chemically and physically
    - Each drug product has unique priming characteristics
  - Canister surface should be inert to formulation components
  - Gaskets and O-rings
    - Should be inert to pressurized organic formulation
    - Should prevent loss of volatile formulation components to ensure the appropriate delivered dose
    - Should prevent contamination by undesirable impurities or environmental components (e.g., oxygen or water) and maintain physical stability
MDIs Have a Complex Drug Delivery Mechanism (2)

- Formulation aerosolization is complex and difficult
  - Result of interaction between formulation and delivery mechanism
  - Drug-specific priming and cleaning requirements
  - Physical characteristics of API and excipients are critical for aerosolization
- Knowledge of optimization needed on:
  - Formulation
  - Container closure and actuator design in presence of formulation
  - Manufacturing process including parameters and controls
  - Packaging
Conclusion

MDIs have a complex drug delivery mechanism because the delivered dose to the patient is critically dependent on formulation composition, formulation components characteristics, and container closure surface condition, composition, and design. The complex drug delivery mechanism presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on safety or effectiveness of the MDI.
MDIs are Complex Dosage Forms

Sophisticated container closure systems are critical to MDIs

- Container (coated metal canister)
- Delivery system (actuator and metering valve)
- Critical tolerances and surface composition
  - Accurately and consistently measure liquid formulation
  - API may adhere to surfaces, which may affect dose delivery
  - Improper materials leach impurities into formulation from plastic and elastomeric components
  - Formulation-container closure physical interactions are complex
- Valve-canister and valve stem seals are critical
  - Canister-metering valve seal held by precisely-crimped ferrule
    - Seals should allow valve stem to move freely
    - Prevent pressurized propellant from leaking as gas
    - Protect from environmental moisture and oxygen
- MDIs should deliver precise quantity/form of API as aerosol to patient airways
MDIs are Complex Dosage Forms (2)

- Unique formulation properties
  - Organic liquid phase – pressurized to 96.6 psi at 25°C (HFA-134a)
  - High energy (unstable) solids in suspension
    - Typically < 5 μm in particle size
    - Results in high surface area of suspended solids
    - Amorphous (non-crystalline) physical form

- Dynamic interactions between container and formulation determine APSD and DDU – critical attributes for safety and efficacy

- Often need protective secondary packaging (foil pouch)
  - Additional protection from moisture and oxygen ingress
  - Necessary when performance deterioration is observed upon storage
  - Need for protective packaging is established by stability studies
MDIs are Complex Dosage Forms (3)

Conclusion
Precise functioning and inert composition of the container closure components, as well as mitigation of the high energy nature of the formulation are necessary to achieving and maintaining necessary performance (emitted dose and APSD) of the dosage form. The complexity of the dosage form presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the MDI.
Bioavailability of Drugs in MDIs is Difficult to Achieve and Assess

- Locally acting MDIs
  - Systemic bioavailability is used to extrapolate to systemic safety
  - To assess local bioavailability of MDI drug products a weight-of-evidence approach includes:
    - clinical endpoint studies
    - pharmacokinetic assessments
  - This approach would present a demonstrable difficulty to compounding.

- Systemic drug delivery through MDIs
  - PK studies in humans are essential to assess the systemic bioavailability
Bioavailability of Drugs in MDIs is Difficult to Achieve and Assess (2)

Bioavailability is complex to achieve and determine

• API PSD, polymorphic form, and other critical physical properties impact absorption

• Absorption obstruction decreases systemic bioavailability

• Currently, in vitro assessments such as APSD and single actuation content, alone, are not sufficient to accurately predict lung deposition, bioavailability, and overall clinical effect.

• Currently there is no single, easily reproducible, reliable method of measurement that can quantitate the dose delivered by the dosage form and received by the patient, which would be necessary to enable the compounder to consistently make product with delivered dose uniformly falling within acceptable ranges.
Bioavailability of Drugs in MDIs is Difficult to Achieve and Assess (3)

Conclusion

- For locally acting drugs applied to the lungs at low doses, measuring local bioavailability does not currently have a single, easily reproducible method of quantitation.
- For systemic drug delivery through MDI drug products, systemic bioavailability is not predictable based on in vitro assessment alone.
- Therefore, achieving and assessing bioavailability of MDIs presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on safety or effectiveness of MDIs.
Compounding of MDIs Requires a Complex Compounding Process

API and Excipient Processing

- It is critical that APIs and excipients for suspension formulations be micronized in specialized equipment followed by conditioning to assure uniformity of the physical form.
- API for solution formulations pose a different problem through degradation, and absorption of the formulation components by the valve components.
Compounding of MDIs Requires a Complex Compounding Process (2)

Formulation Compounding

- Overall unit-to-unit and batch-to-batch uniformities are dependent on the variability of the formulation filled into the canisters.
- Formulation filled is dependent on the uniformity of the bulk formulation in the filling system, the blend uniformity of the solids, and the rate of addition of make-up propellant.
- Filling can be accomplished with the formulation cold or under pressure.
- For both process types:
  - Complex requirements for uniform filling.
  - Critical to control moisture, which is challenging
Compounding of MDIs Requires a Complex Compounding Process (3)

Formulation Compounding

• Both filling types use equipment specialized for MDI manufacturing such as:
  – Homogenizer
  – Sealed formulation tank
  – Sealed filling tank
  – Formulation circulation system to maintain suspension uniformity
  – Rotary or stationary filling unit with purge, crimping, and filling heads

• Manufacturing equipment is difficult to set up and validate because of large number of process parameters involved.

• Specialized equipment is necessary to assure uniformity in both particle size and concentration, which affects safety and efficacy.
Compounding of MDIs Requires a Complex Compounding Process (4)

Formulation Compounding

• Changes in polymorphic form and PSD during liquid formulation blending and filling are possible when:
  – API has solubility in an intermediate formulation
  – Blending is not accomplished at sufficiently low temperature

• Measurement of the bulk formulation properties during filling is difficult since a sealed and pressurized system is used for both filling types.

• A sealed and pressurized filling system is crucial to prevent:
  – Ingress of moisture or oxygen
  – Loss of volatile propellant or co-solvent
Compounding of MDIs Requires a Complex Compounding Process (5)

Formulation Compounding

• Ingress of moisture or oxygen or loss of volatile components should be minimized to prevent:
  – Changes in the API PSD
  – Increased propensity of the API to interact with the container closure components.

• Changes in the extent of these interactions may cause significant batch-to-batch variability and have a deleterious effect on safety and efficacy.
Compounding of MDIs Requires a Complex Compounding Process (6)

Filling and Valve Sealing

- Formulation filling into the MDI is a critical and complex procedure which includes:
  - Either evacuation or purging of the container closure with propellant to eliminate atmospheric moisture and oxygen
  - Sealing of the valve to the canister by precise crimping
  - Filling of the formulation into the canister.

- Critical filling parameters to assure batch-to-batch uniformity include:
  - Propellant purge weight
  - Crimping dimensions
  - Fill volume (for cold-fill operations),
  - API content uniformity in the formulation
  - Assay
  - Pressure testing when co-solvents or propellant mixtures are used.
Compounding of MDIs Requires a Complex Compounding Process (7)

Conclusion
Any errors in filling or formulation compounding are reasonably likely to result in delivered dose variability in either the quantity of the emitted drug or its APSD. Insufficient drug delivered to the appropriate part of the lungs (as measured by these two parameters) would pose an efficacy concern, and potentially a safety concern, especially for rescue medications. Compounding an MDI involves a complex compounding process that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the MDI.
MDIs Require Complex Physicochemical or Analytical Testing

- MDIs need extensive characterization and development studies to test the:
  - Formulation
  - Container closure and its compatibility with formulation
  - Manufacturing process

- Development of specifications and in-process controls for the following is critical since these ultimately determine performance characteristics
  - Raw materials
  - Container closure components
  - Manufacturing consistency
MDIs Require Complex Physicochemical or Analytical Testing (2)

Raw Materials Testing

• Appropriate API specifications (release, stability, retest)
  – Before and after additional processing (micronization and conditioning)
  – Controls are needed to maintain consistent API physicochemical properties, such as:
    • Polymorphic form
    • Particle size distribution
    • Surface morphology
    • Water content etc.

• Helps to ensure consistent dosage form performance
  – Physical stability of the formulation
  – Drug content per actuation (Assay and DDU)
  – Aerosol APSD for delivered drug
  – Control of the above attributes helps to assure consistent bioavailability
MDIs Require Complex Physicochemical or Analytical Testing (3)

In-process Testing

- Low drug load in suspension (typically 0.1-5 µg/mL) is common and could lead to a non-uniform drug product
- Difficult to sample in the pressurized system
- Unit testing after filling is necessary to ensure accurate and consistent dose delivery. Testing should include:
  - Assay
  - Valve crimp measurements
  - Component fill weight
  - Function and integrity testing
- Low drug loading makes periodic in-process testing necessary to assure proper suspension uniformity for unit filling
MDIs Require Complex Physicochemical or Analytical Testing (4)

Lot Release Testing

• APSD – most critical performance attribute
  – Needs cascade impactor analysis of dose delivered
  – Complex procedure with low masses of API analyzed, may be in excipient matrix
  – Difficult to use and qualify compared with other analytical methods

• Leachables testing is critical for safety:
  – Needs to test for impurities from container closure components
  – Complicated by leaching over time by liquid organic formulation
  – Uses sensitive specialized analytical techniques (ppm and ppb levels)
  – Should be able to quantitate a wide range of chemical structures with multiple methods

• Delivered Dose Uniformity
  – Another critical performance attribute
  – Testing needs a special apparatus and support equipment
MDIs Require Complex Physicochemical or Analytical Testing (5)

Stability Testing

- Quality and performance testing covers:
  - Appropriate storage conditions
  - Performance testing at beginning and end of product life
- In-use period testing includes:
  - Characterization studies (product specific)
  - Determination of in-use period (after exposure until labeled number of actuations, i.e., beginning and end of shelf life)
  - Resting time and priming requirements (non-use)
  - Cleaning requirements
  - Temperature and humidity cycling (shipping)
MDIs Require Complex Physicochemical or Analytical Testing (6)

**Conclusion:** MDIs require complex physicochemical and analytical testing because the formulation properties and critical performance parameters of the product require complex analytical devices and procedures. Furthermore, impurities must be quantitated through various sensitive analytical techniques developed specifically for these impurities.

In-process testing of MDIs and control of their manufacturing process, using methods unique to MDI manufacturing procedures, are critical to minimize unit-to-unit and batch-to-batch variability, and to ensure accurate performance throughout the product shelf life and in-use life.

The physicochemical or analytical testing needed for MDIs is so complex that it is likely that a product quality defect would not be detected, which would lead to an adverse effect on the safety or effectiveness of the compounded drug. Accordingly, the complex testing required for MDIs presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on safety or effectiveness of the MDI.
Proposal

Based on an analysis of the evaluation criteria to assess if MDIs present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product and that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the category of drugs, taking into account the risks and benefits to patients, we propose that MDIs be included on the list of difficult to compound drug products under sections 503A and 503B of the FD&C Act.
Dry Powder Inhalers (DPIs)

Pharmacy Compounding Advisory Committee Meeting
March 9, 2016

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Overview of Presentation

• DPI Background Information
• Evaluation Criteria for DPIs
  – Complex Formulation
  – Complex Drug Delivery Mechanism
  – Complex Dosage Form
  – Bioavailability
  – Complex Compounding Process
  – Physicochemical or Analytical Testing
• Proposal
DPI Background

- DPIs deliver powder formulations topically to the tissue surfaces of the lungs
- Most DPIs are designed for local effect in the lung
  - Systemic drug absorption into the bloodstream from the lung is generally undesirable (although larger drug particles may still be swallowed and have oral bioavailability and related side effects)
  - Most common use is for treatment for asthma and chronic obstructive pulmonary disease (COPD)
  - Other uses include treatment of
    - Cystic fibrosis
    - Lung infections
    - Systemic drug delivery (e.g., insulin for diabetic patients)
DPI Background (2)

- DPIs consist of formulated drug(s) and an associated, specific device for delivery of drug by inhalation
- Two main sub-types
  - Pre-metered
  - Device-metered
- Proprietary device designs vary widely from relatively simple to complicated
- Drug substances (or active pharmaceutical ingredients or APIs) are micronized to small particle size (typically < 5 μm)
- Due to low doses of drugs typically used, formulations generally use carrier excipients for the micronized API (bulking agent) to provide acceptable dosing uniformity
- Energy for delivery and deagglomeration (release of API from carrier) of the formulation typically comes from patient inhalation maneuver
- Formulations often have reduced stability relative to those of more common drug products, due to the finely micronized API (high energy state)
- Formulation, production, and associated control strategies are unique for DPIs
- Inadequate control strategies can result in inconsistent performance and non-optimum dosing of patients
DPI Background – Operating Principle (3)

Formulation

Metering

Pulmonary delivery

Modified from Telko MJ, Hickey AJ. Respir Care 2005;50:1209-27
DPI Background (4)

• DPIs are designed to deliver a metered aerosol of drug powder to lungs by oral inhalation
  – Deliver small precise amounts of drug (as little as a few micrograms up to ~1 milligram per device actuation)
  – Consistent dosing (amount and particle size) of drug
    • Critical for safety and efficacy
    • Helps ensure correct deposition site in lungs
  – Critical quality control performance test attributes to help assure consistent dosing:
    • Delivered dose uniformity (DDU)
      – Measure of dose-to-dose quantity of drug emitted for deposition in airway and expected dosing variability under ideal/laboratory circumstances
      – Can be affected by manufacturing, formulation, DPI device
    • Aerodynamic particle size distribution (APSD)
      – Measures the quantity of drug with ranges of known aerodynamic particle size
      – Results relate to site of deposition in airways; however, the relationship can rarely be established with any confidence
      – Helps assure necessary range of API particle sizes typically required (< 5 μm) and is a measure of API PSD and formulation consistency
      – Also can be affected by manufacturing, formulation, DPI device
DPIs Have Complex Formulations

Development

• API/excipient interactions depend on both the choice of excipients and controls for API/excipient physicochemical properties
• The API/excipient interactions help assure:
  – Sufficient physicochemical stability (adhesion) to the formulation
  – Substantial and consistent deagglomeration of the API from the excipients during delivery to assure reproducible dose performance
  – Adequate formulation manufacturability (e.g., flowability, reduces presence of API fines), which improves:
    • Reproducible device filling or pre-metering
    • Decreased drug losses to manufacturing equipment
  – Formulation robustness, even with high variability associated with patient-driven dose delivery
• Carrier excipients are also necessary with low drug loads (< 1 mg/actuation) to achieve acceptable dose uniformity
DPIs Have Complex Formulations (2)

Components
• Characterization and control of formulation component properties are critical to yield DPIs with consistent dosing performance and stability, helping to assure safety and efficacy for patients
  – API properties
    • Particle size distribution (PSD)
      – Consistent fine API is necessary to reach the site of action
      – Fine API has high surface area (energy); often requires unique treatment, handling, and formulation processes
    • Solid state (crystalline) form of API determines kinetic solubility and bioavailability at the site of action
    • Special conditioning is often needed to reduce the percentage of amorphous API resulting from micronization, increasing API physicochemical stability
DPIs Have Complex Formulations (3)

Components, cont.

- Excipient properties
  - Few API carrier excipients are qualified for oral inhalation, and purity is critical for safety
  - Excipients (e.g., lactose) need to be compatible with API to assure chemical stability
  - Carrier surface stabilizers are often necessary to dampen high energy interactions of carrier and fine API and achieve needed balance of API/carrier interparticulate interactions
    - Yield formulations producing higher and consistent amounts of fine particles of API with dose delivery
    - Increases shelf-life of drug product
  - High level of purity of APIs/excipients necessary for oral inhalation route of administration
    - Requirements for purity have not been addressed by current compendial API/excipient monographs
    - Patients with diseased lungs are often more sensitive to formulation impurities
DPIs Have Complex Formulations (4)

**Formulation Stability**

- Unusually consistent and stable formulations are critical to DPIs to prevent dosing variability (sub- or supra-therapeutic dosing)
- Formulation stability can be affected by API and excipient properties
  - Recrystallization of amorphous material from micronization can lead to particle bridging and change in APSD
  - Changing API polymorphic form can alter drug kinetic solubility (alter topical lung bioavailability)
- Extensive formulation development and characterization studies are necessary
  - Determine need for stability additives or component conditioning
  - Helps assure formulation stability with optimized drug load
  - Increase ability to achieve blend uniformity
**Conclusion**

DPIs have complex formulations that require extensive development, characterization, and controls to assure acceptable dosing performance, and the complex formulations present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.
DPIs Have Complex Drug Delivery Mechanisms

• Unlike most drug products, dosing of drug from DPIs normally depends on the patient inhalation maneuver (i.e., patients are a part of the drug delivery mechanism)
  – Patient inhalation withdraws drug formulation from the delivery device
  – Patient inhalation deagglomerates (or breaks up) the formulation to yield inhalable-sized API particles
  – Patient inhalation parameters (speed of air flow rise, peak flow, etc.) can vary widely
    • patient-to-patient
    • or day-to-day for a single patient
  – DPI designs (device/formulation) need to be optimized to be robust to varying patient inhalation parameters (and not contribute to dosing performance variability)

• Ideal DPI device designs are:
  – Intuitive to use
  – Robust, in conjunction with formulation, to variable patient inhalation parameters
  – Rugged to manipulation, use, unintentional misuse (e.g., dropping), and expected storage and shipping conditions
  – Informative of the remaining number of doses
  – Limited device hold-up of high energy (micronized) drug (i.e., limited adherence to inhaler components, reduce cleaning requirements)
DPIs Have Complex Drug Delivery Mechanisms (2)

- Since drug delivery depends on patient-usage conditions (inherently variable), extensive data are critical to characterize the drug product and create patient-oriented labeling (instructions-for-use/storage conditions) to limit drug delivery variability with patient use, as much as possible. Characterization studies include examination of:
  - Stability of formulation after removal of protective packaging
  - Behavior of DPI after undesirable storage or environmental exposure
  - Impact of patient use on remaining doses in DPI
  - Effect of orientation of DPI during use (both loading and delivery of dose)
  - Drug loss to device and necessary cleaning procedure to assure continued reproducible dosing
  - Drug available near exhaustion (device-metered DPIs without lockout)
  - Effect of varying flow rate on dosing performance considering typical patient generated flow-rates (dependent on device resistance to air flow)
  - Device ruggedness (e.g. misuse, dropping, shipping)
DPIs Have Complex Drug Delivery Mechanisms (3)

Conclusion

DPIs have complex drug delivery mechanisms as they must be designed with formulations and associated devices that in combination provide consistent drug delivery (dosing and APSD) to patients with widely varying inhalation characteristics.

DPIs have a complex drug delivery mechanism that present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.
DPIs Are Complex Dosage Forms

Regardless of the underlying complexity of their devices:
• DPI dosage forms have complex formulations
• DPI dosage forms have complex drug delivery mechanisms
• DPIs must be designed to perform reproducibly with variation inherent to patient inhalation-driven dosing

Conclusion
DPIs are complex dosage forms that present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.
Bioavailability of Drugs in DPIs is Difficult to Achieve and Assess

• Locally acting DPIs
  – Systemic bioavailability is used to extrapolate to systemic safety
  – To assess local bioavailability of DPI drug products a weight-of-evidence approach typically includes:
    • clinical endpoint studies
    • pharmacokinetic assessments
  – This approach would present a demonstrable difficulty to compounding.

• Systemic drug delivery through DPIs
  – PK study in humans is essential to assess the systemic bioavailability
Bioavailability of Drugs in DPIs is Difficult to Achieve and Assess (2)

- Bioavailability is complex to determine
- API PSD, polymorphic form, and other critical physical properties for the formulation likely impact absorption
- Absorption obstruction decreases systemic bioavailability
- Currently, in vitro assessments such as APSD and single actuation content, alone, are not sufficient to accurately predict lung deposition, bioavailability, and overall clinical effect.
- Currently there is no single, easily reproducible, reliable method of measurement that can quantitate the dose delivered by the dosage form and received by the patient, which would be necessary to enable the compounder to consistently make product with delivered dose uniformly falling within acceptable ranges.
Bioavailability of Drugs in DPIs is Difficult to Achieve and Assess (3)

Conclusion

• For locally acting drugs applied to the lungs at low doses, measuring local bioavailability does not currently have a single, easily reproducible method of quantitation.

• For systemic drug delivery through DPI drug products, the systemic bioavailability is not predictable based on in vitro assessment alone.

• Therefore, achieving and assessing bioavailability of DPIs presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on safety or effectiveness of DPIs.
DPIs Require Complex Compounding Processes

- DPIs necessitate API with small particle size for inhalation
  - Typically APIs are micronized with specialized equipment (< 5 μm)
  - Further conditioning may be needed to control physical properties of micronized API to achieve desired performance reproducibility and formulation stability
- Typical low drug loading needs extra care during processing to achieve adequate blend uniformity
- Specialized seal integrity in-process testing is necessary to help assure functionality of any protective packaging
DPIs Require Complex Compounding Processes (2)

- Optimizing formulation characteristics for device filling and drug product usage may require additional processing/manufacturing considerations
  - Use of formulation stabilizers (e.g., lubricants, fine carrier particles) to achieve necessary API/excipient interaction balance crucial to dosing performance and stability
  - Control of excipient physicochemical properties and particle size
  - Determine the need for additional environmental controls during manufacture and/or application of DPI protective packaging (e.g., desiccant, oxygen scavenger, foil overwrap)
DPIs Require Complex Compounding Processes (3)

Conclusion
Manufacturing a DPI requires substantial development to understand the optimal formulation, manufacturing, and device characteristics necessary to provide a robust drug product that can provide the accurate and precise dosing of patients with widely varying inhalation characteristics.

Any errors in formulation compounding and device filling are reasonably likely to result in delivered dose variability in either the quantity of the emitted drug or its APSD. Such scenarios could result in insufficient or excessive drug delivered to the appropriate parts of the lungs, potentially leading to lack of efficacy or other patient safety concerns.
DPIs Require Complex Compounding Processes (4)

Conclusion
Compounding a DPI involves a complex compounding process that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.
DPIs Require Complex Physicochemical or Analytical Testing

- In addition to routine tests applied to most drug products, some critical DPI quality control testing is unique, complex, and specialized:
  - Drug product component testing for DPIs is a critical part of the overall quality control strategy to ensure DPI dosing performance and low variability
    - Physical stability of the formulation
    - Drug content in formulation and per actuation (assay and DDU)
    - Aerosol APSD for delivered drug
    - API/excipients testing includes
      - Crystalline form/amorphous content
      - PSD
      - Particle surface texture, surface area
      - Moisture content
DPIs Require Complex Physicochemical or Analytical Testing (2)

- Device/Packaging testing
  - Dimensional measurements of certain critical components (e.g., components that meter drug formulation in device-metered DPIs)
  - Testing to help assure consistency of composition and surface characteristics of components in the flow path of the exiting drug formulation (i.e., to decrease API hold-up variability)
  - Functional testing (e.g., dose counter function); crucial for asthma rescue medication DPIs
  - Moisture vapor transmission rate (MVTR) testing to gauge protective capability of foil pouch or similar material
DPIs Require Complex Physicochemical or Analytical Testing (3)

- DPI lot release and stability testing for key performance-related parameters include those for:
  - Aerodynamic PSD
    - A critical quality control test attribute of DPIs
    - Requires cascade impactor (CI) analysis of dose delivered (specialized equipment and analyst training)
    - Complex procedure with low masses of API analyzed; sensitive methods required
    - DPIs present particular challenge due to particle “bounce” and reintrainment
    - Difficult to perform and validate compared with other analytical methods
    - CI equipment requires specialized handling and maintenance
  - Delivered dose uniformity (DDU)
    - A critical quality control test attribute of DPIs
    - Testing uses specialized equipment and analyst training
  - DPI stability testing for the above and other parameters
    - Determines appropriate storage conditions
    - Sets the drug product expiration dating period
    - Qualifies protective packaging
DPIs Require Complex Physicochemical or Analytical Testing (4)

- Extensive drug product characterization laboratory testing to create patient-oriented instructions-for-use and labeled storage conditions are routinely performed
  - In-use period (with protective packaging)
  - Temperature cycling (environmental/storage considerations)
  - Effect of patient use (testing returned partially used drug product)
  - Orientation effects
  - Drug hold-up and cleaning requirements
  - Drug available near exhaustion (device-metered)
  - Effect of varying flow rate on dosing performance
  - Device ruggedness testing (misuse, shipping, etc.)
Conclusion

The quality control testing of component materials, both prior to and during manufacture, and the final testing of finished DPI drug product for lot release and stability characterization has a complex methodology to help assure the critical quality attributes related to dosing performance are attained. These tests are difficult to develop, validate, and perform routinely, use highly specialized and unique equipment, and analysts that have received considerable training. Accordingly, the complex testing for DPIs presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.
Proposal

- Based on an analysis of the evaluation criteria to assess if DPIs present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product and that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the category of drugs, taking into account the risks and benefits to patients, we propose that DPIs be included on the list of difficult to compound drug products under sections 503A and 503B of the FD&C Act.