# Dimercapto-1-propanesulfonic Acid (DMPS)

**Pharmacy Compounding Advisory Committee Meeting**

**June 23, 2016**

**Kathy Robie Suh, MD, PhD**
**Clinical Team Leader**
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products (OHOP)

# DMPS
# Review Team

**George Shashaty, MD**, Medical Officer, DHP/OHOP

**Kathy Robie Suh, MD, PhD**, Clinical Team Leader, DHP/OHOP

**Brenda J. Gehrke, PhD**, Pharmacologist, DHOT/OHOP

**David Lewis, PhD**, Chemist, DPMAI, OLDP, OPQ

**Ann Farrell, MD,** Director, DHP/OHOP

**Norman R. Schmuff, PhD**, Associate Director for Science, OPF

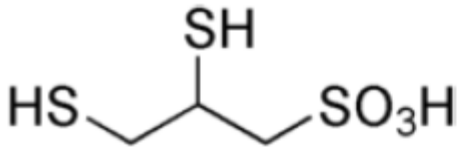
**Christopher M. Sheth, PhD**, Team Leader, DHOT/OHOP

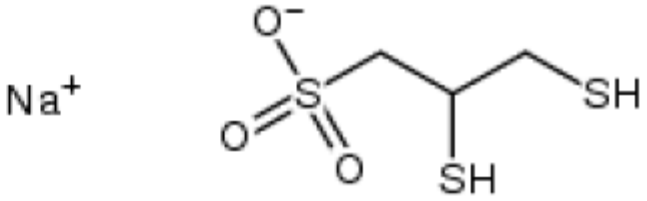
**John K. Leighton, PhD, DABT**, Division Director, DHOT/OHOP

# DMPS: Nomination

- Use: “for treatment of heavy metal poisoning.”
- Route of administration: Oral, Intravenous injection, intramuscular injection.
- Materials received
  - Publications of anecdotal reports and mostly uncontrolled series of cases of exposure to various heavy metals treated with DMPS.

# DMPS: Chemistry*




- Most commonly supplied as its sodium salt.
- Non-hygroscopic, exists as monohydrate.
- MW-228.3 Daltons.
- Stable in the crystalline form.
- Relatively stable in aqueous solutions, but labile to oxidation.

* Information based on Heyl Scientific Product Monograph

# DMPS: Chemistry (cont) *

- Purified by release from the lead salt.
- Potential in process impurities: lead, allyl bromide, allyl sulfonic acid, and 2,3-dibromopropane-1-sulfonic acid.
- Potential heavy metal contamination can be monitored using USP compendial methods.

* Information based on Heyl Scientific Product Monograph.

# DMPS: Nonclinical*

- Pharmacology
  - Mechanism of action not fully characterized.
  - Increases the urinary elimination of arsenic and interferes with arsenic methylation.
  - Promotes excretion and protects against mercury-induced renal damage by inhibiting mercury accumulation in renal proximal and distal tubular cells.
- Toxicokinetics
  - Oral absorption 30% in rats and 60% in dogs with peak plasma concentrations reached after 30 to 45 minutes.
  - Distribution after IV dose mainly into plasma and kidneys.
  - Elimination renal with a serum half-life of about 20 to 60 minutes.

* Based on April 2009 WHO document and Heyl monograph

# DMPS: Nonclinical (cont)*

- Safety pharmacology
  - Relatively low acute toxicity; LD50 for parenteral administration approximately 1 to 2 g/kg.
  - Relatively low chronic toxicity in dogs and rats.
  - No evidence of adverse effects on cardiovascular, gastrointestinal, or renal systems.
  - No data available on central nervous system or respiratory system.
- Not mutagenic in the Ames test.
- No reproductive toxicity or teratogenicity shown in animals.
- Information on carcinogenicity is not available.

* Based on April 2009 WHO document and Heyl monograph.

# DMPS Safety: Major Associated Adverse Reactions

- Serious case of Stevens-Johnson reported; one death due to severe diffuse desquamation.
- Dermatologic reactions, nausea and vomiting, hypotension, increases in serum transaminases, transient bronchospasm, fever, leukopenia.
- Reactions typically mild or moderate in severity.

# DMPS: Clinical Evaluation of Effectiveness

- Uses in published studies and reports include for high arsenic in drinking water, lead poisoning, mercury poisoning, mercury excess from facial cream, mercury-containing dental amalgams, Wilson's disease, high bismuth.
- Most reports are of uncontrolled use or anecdotal reports.
- Literature search found no adequate scientific studies that demonstrate the effectiveness of DMPS for the reported uses.

# FDA Approved Drugs for Treatment of Heavy Metal Poisoning

- Multiple available approved drugs for treatment of heavy metal poisoning
  - Calcium disodium versenate (edetate disodium calcium) – lead.
  - Chemet (2,3,-dimercaptosuccinic acid; succimer; DMSA) – lead.
  - BAL (British Anti-Lewisite; dimercaprol) – arsenic, gold, mercury.
  - Cuprimine (penicillamine) – Wilson's disease, cystinuria, severe active rheumatoid arthritis.
  - Syprine (trietine dihydrochloride) – Wilson's disease (2$^{nd}$ line).

# DMPS: Historical Use in Compounding

- Reported at 1998 PCAC that compounding dates to mid-1980s.
- Clinical use of DMPS mentioned in literature as early as 1958.
- Internet search suggests main "intended uses"
  - Treatment of persons with presumed mercury toxicity due to mercury amalgam dental fillings.
  - Treatment of persons with autistic disorders.

# Conclusions

- DMPS is well defined and can be identified consistently, but manufacture may leave residual impurities, including lead which is toxic.
- Clinical investigation of use of the DMPS has been inadequate to establish safety.
- No clear evidence for clinical benefit of DMPS as currently used.
  - FDA-approved medications are available for treating heavy metal poisoning.
- Historical use dating to 1950s.

# Recommendation

- We recommend that DMPS ***not 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.