

# Melatonin

## **Pharmacy Compounding Advisory Committee Meeting June 9, 2021**

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# Melatonin Evaluation Team

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**Special thanks to:**

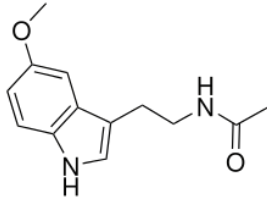
Division of Psychiatry in the Office of New Drugs

# Nomination

- Melatonin is a hormone that was nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Melatonin was proposed for the treatment of sleep disorders in patients with autism spectrum disorder (specifically children and adolescents) in doses ranging from 0.2 mg - 5 mg for oral administration
  - The discussions of the use of melatonin in the other pediatric populations and in certain adult populations were included in the Appendix section of the evaluation as background information. However, the other uses were not considered for the overall assessment and recommendation

# Physical and Chemical Characterization

- Small molecule hormone



- Melatonin is easily characterized with various analytical techniques and the preparation of this substance has been well developed

## Physical and Chemical Characterization (2)



- Levels of impurities in the final bulk substance need to be carefully monitored
  - Because reagents such as alkyl halides and aldehydes are likely to be involved in the synthesis, these may present structural alert for mutagenicity

### **Conclusion:**

Melatonin is likely to be stable under ordinary storage conditions in solid dosage forms

With protection from oxygen (air), light and proper formulation components, a relatively stable liquid formulation of the drug substance can be achieved

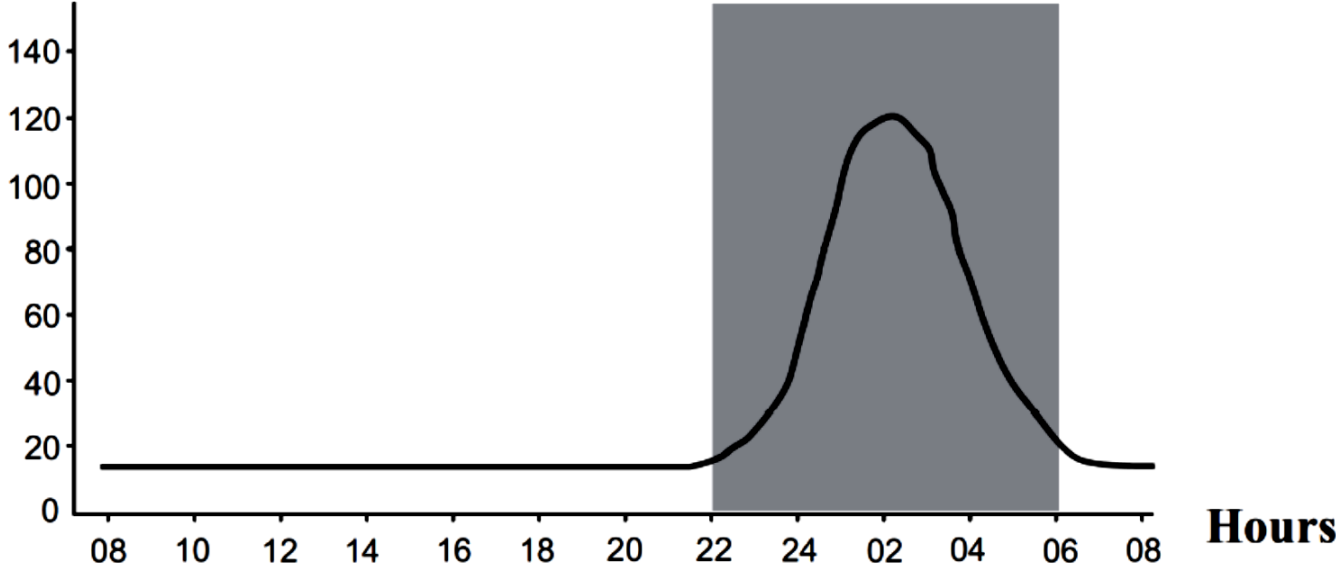
# General Pharmacology



- Neurohormone synthesized in the pineal gland in mammals
  - The suprachiasmatic nucleus in the hypothalamus regulates melatonin synthesis and secretion
- Melatonin plays a key role in regulating the sleep–wake circadian rhythm
- Melatonin synthesis is associated with circadian rhythms and circulating melatonin levels can impact sleep patterns
  - During daylight hours the levels of melatonin are low
  - During nighttime plasma melatonin levels rise rapidly

# Circadian Profile of Endogenous Melatonin

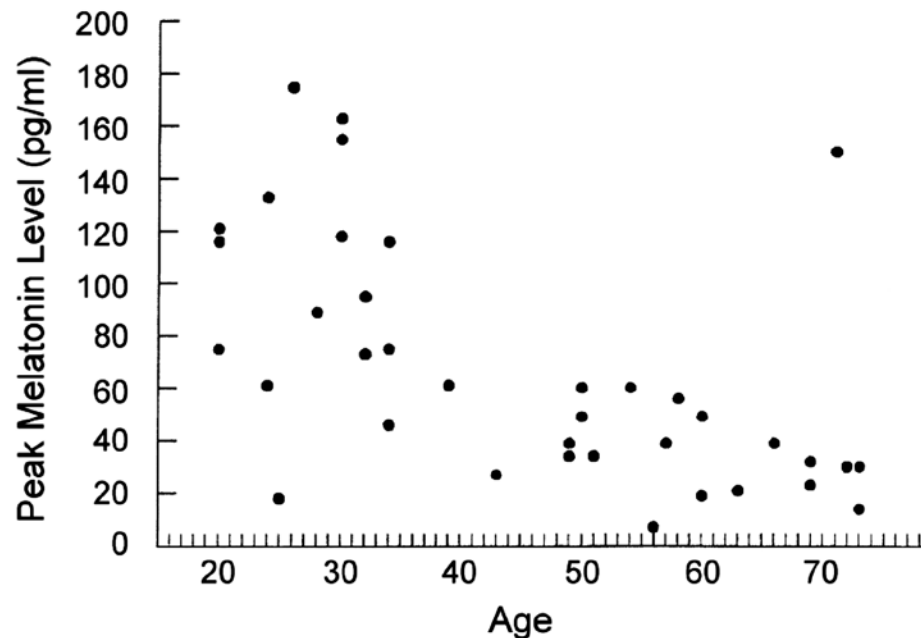
**Melatonin (pg/mL)**



The shaded area represents the hours after sundown  
Source: Tordjman et al.2017

# Endogenous Melatonin

- Melatonin secretion varies by age and depends on the time of day for peak secretions
  - Levels lower in adults than in children
- Children with neurodevelopment disorders do not have normal physiological production of melatonin
  - lower mean concentrations of melatonin during the dark phase of the day (i.e., from 8pm to 8am)



Night-Time Peak Serum Melatonin Levels in Subjects of Different Ages (Years)  
 Source: Wurtman 2005



# Clinical Pharmacology - Exogenous Melatonin



- Melatonin is highly lipid soluble, diffuses freely across cell membranes into all tissues, and is found in the blood largely bound to albumin
- Melatonin undergoes first-pass metabolism in the liver before it is excreted in the urine or saliva
  - Melatonin is initially oxidized to 6-hydroxy melatonin by a cytochrome P450-dependent microsomal oxidase and then conjugated to 6-sulfatoxymelatonin, the major metabolite of melatonin
- Primarily metabolized by CYP1A2 and CYP2C19; inhibitors of CYP1A2 may increase melatonin concentrations

## Clinical Pharmacology – Exogenous Melatonin (2)



- Low bioavailability (approximately 15%) and inter-individual variability
- $T_{\max}$  was 50 minutes following ***oral immediate-release*** formulations of melatonin
- $T_{1/2}$  was 45 minutes in both the oral and IV routes of administration
- Melatonin PK depends on the dosage form (immediate/fast-release or controlled/prolonged-release, etc.)

# Nonclinical Safety

- Acute toxicity
  - No major toxicities and overall a low toxicity profile in rodent models
  
- Repeat oral dose toxicity
  - 28-day study in rats (up to 7.3 mg/kg/day) did not show adverse drug related effects
  - 90-day study in rats (up to 200 mg/kg/day) did not impact survival, terminal body weights or organ weights
  - 13-week and 26-week study in rats (75 and 150 mg/kg/day) showed increased hemoglobin concentrations and platelet counts (13-week time point), increased liver weights (13-week time point) and minor centrilobular hepatocytic hypertrophy (13 and 26-week time points)

## Nonclinical Safety (2)

- A 70-day juvenile toxicity study in rats (160 mg/kg/day) showed no deaths or drug related effects on body weight, ophthalmology, central nervous system, estrous cyclicity, sexual maturity, sperm parameters or macroscopic changes
  - Source: European Medicines Agency's (EMA) assessment of melatonin prolonged-release minitablets (Slenyto; approved on July 26, 2018); indicated for treating insomnia in 2 to 17-year-old children and adolescents with autism spectrum disorder, in addition to approval for use in patients with Smith-Magenis syndrome

## Nonclinical Safety (3)

- Genotoxicity
  - Standard panel of genotoxicity assays did not show a genotoxic signal for melatonin
- Reproductive and Developmental toxicity
  - No embryofetal toxicities in rats
  - Some skeletal malformations (absence of lung or iliac alignment and caudal shift of vertebrae) were noted in the rabbit at 150 mg/kg/day
- Carcinogenicity
  - Increased incidence of non-neoplastic pituitary adenomas seen in male rats at 150 mg/kg/day
  - Increased incidence of thyroid tumors among male rats (41% in 75 mg/kg/day and 42% in 150 mg/kg/day compared to 10% in controls)
  - Increased incidence of thyroid tumors in females dosed (45% in 75 mg/kg/day group and 28% in 150 mg/kg/day compared to 2% in controls)

# Clinical Safety – FAERS



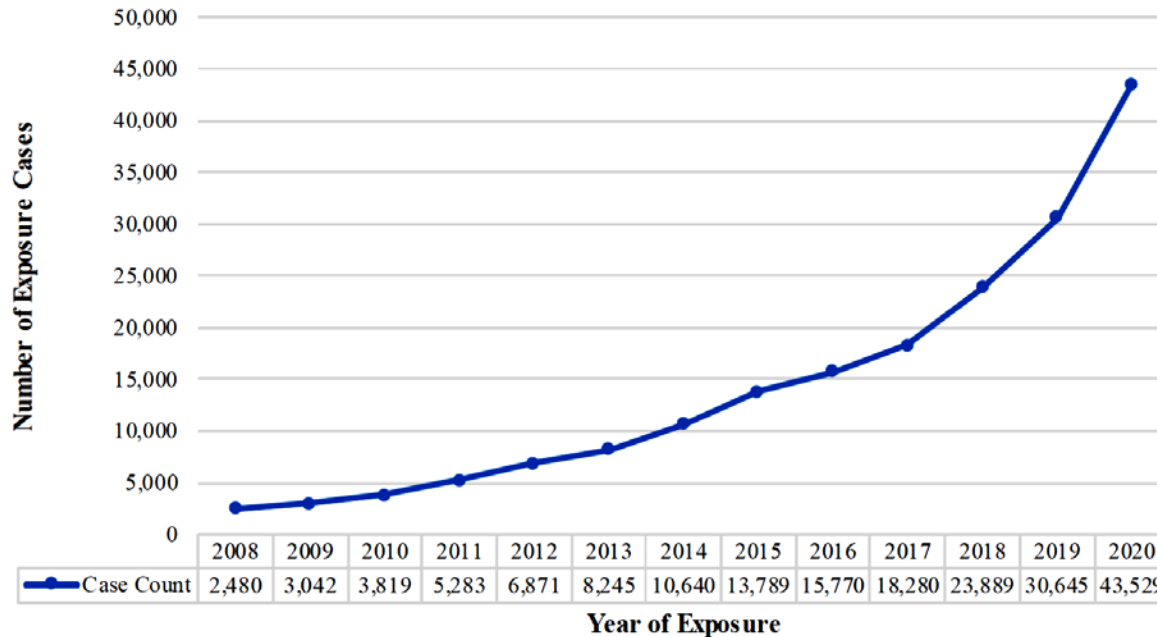
- FDA Adverse Event Reporting System, FAERS reported adverse events were consistent with the known safety profile of melatonin including information discussed in the literature
  - The reports included cases in children with autism spectrum disorder
- The FAERS reported adverse events primarily consisted of acute reactions to short term exposure rather than exposure data for longer-term effects
- Few serious FAERS events identified
  - The information was confounded by use of melatonin with concomitant medications, comorbid disease state, possible drug-drug interactions, or lacked enough details precluding the ability to determine a drug-event association

## Clinical Safety – FAERS (2)

Three patients reported melatonin use for sleep disorder in autism spectrum disorder or neurodevelopmental disorder:

- 16-year-old male with Asperger’s syndrome used melatonin to treat insomnia from the use of methylphenidate (dose, duration not reported) experienced restlessness, mild dysphoria, hallucinations, lightheadedness, and insomnia after taking 3 mg melatonin once daily. Melatonin was discontinued, and the AEs resolved (positive dechallenge). It was not clear whether methylphenidate was discontinued
- 8-year-old female with ADHD, neurodevelopmental disorder, and sleep disorder received melatonin 5 mg daily at bedtime for one year. She was reported to have “recently” switched from lisdexamfetamine to methylphenidate. She experienced irritability and agitation one month after an increase in dose of methylphenidate. Methylphenidate dose was decreased and patient experienced difficulty falling asleep, hallucinations, and suicidal thoughts. Methylphenidate was discontinued, and melatonin was continued. The outcome was not reported
- 10-year-old male with autism spectrum disorder was on melatonin 3 mg daily at bedtime for 3-4 years. He had a 2-year history of abdominal pain, heartburn, dysphagia, and an endoscopy revealed eosinophilic esophagitis. He also experienced muscle aches. The outcome was not reported

# Clinical Safety – AAPC NPDS



The American Association of Poison Control Centers’ (AAPCC) National Poison Data System (NPDS) The number of melatonin-involved exposure cases documented by U.S. poison control centers per year from January 1, 2008 – December 31, 2020 (N=186,282) that included aggregate counts per year with single product containing melatonin alone The figure demonstrates a steady increase in reports over the past seven years



# Clinical Safety - CAERS

- CFSAN Adverse Event Reporting System (CAERS)
  - 238 reports; 142 cases reported information for at least one medically important event, 81 cases reported hospitalization and 14 cases reported life threatening outcomes
  - Majority of cases were confounded by multiple treatments, because of the number of other ingredients in the melatonin product, and/or underlying disease or there was insufficient information for assessment

# Clinical Safety – Clinical Trials

Adverse event	No. studies	Melatonin subjects with AE (AE <sub>MLT</sub> )	Placebo subjects with AE (AE <sub>PLB</sub> )	Subjects with AE corrected for placebo (AE <sub>MLT</sub> – AE <sub>PLB</sub> )	AE frequency (%) corrected for placebo
Daytime sleepiness <sup>a</sup>	9	50	23	27	1.66
Headache	15	44	32	12	0.74
Other sleep-related AEs <sup>b</sup>	6	21	9	12	0.74
Dizziness	4	14	2	12	0.74
Hypothermia <sup>c</sup>	2	14	4	10	0.62
Decreased appetite	3	7	1	6	0.37
Restlessness	2	6	0	6	0.37
Rash <sup>d</sup>	4	15	9	6	0.37
Burping	1	5	0	5	0.31
Tearfulness	1	5	0	5	0.31
Fatigue	3	25	21	4	0.25
Seizures (not increased rate)	2	12	8	4	0.25
Insomnia <sup>e</sup>	4	7	4	3	0.18
Gastrointestinal illness/diarrhoea	3	10	7	3	0.18
Muzziness/fuzzy feeling/hung-over	3	3	0	3	0.18
Hyperactivity	2	4	1	3	0.18
Enuresis	1	3	0	3	0.18

Source: Besag, FMC, MJ Vasey, KSJ Lao, et al., 2019, Adverse Events Associated with Melatonin for the Treatment of Primary or Secondary Sleep Disorders: A Systematic Review, CNS Drugs, 33(12):1167-1186

# Clinical Safety – Clinical Trials

## (Melatonin in Children with Autism Spectrum Disorder)

**TABLE S2** Most Commonly Reported Treatment-Emergent Adverse Events (AEs) (Safety Set)

	Double-blind phase (13 weeks)				Open-label phase (91 weeks)	
	PedPRM		Placebo		All PedPRM	
	Participants (n = 60)	Events	Participants (n = 65)	Events	Participants (n = 95)	Events
Participants with at least 1 TEAE	51 (85.0%)		50 (76.9%)		80 (84.2%)	
Total number of AEs		208		156		524
AEs reported by ≥10% participants						
Somnolence	17 (28.3%)	18	8 (12.3%)	8	24 (25.3%)	31
Rate of somnolence events per participant per 1 year of treatment <sup>a</sup>		1.2		0.49		0.19
Fatigue	15 (25.0%)	19	12 (18.5%)	13	25 (26.3%)	33
Rate of fatigue events per participant per 1 year of treatment <sup>a</sup>		1.27		0.8		0.20
Mood swings	10 (16.7%)	10	11 (16.9%)	12	17 (17.9%)	24
Rate of mood swings events per participant per 1 year of treatment <sup>a</sup>		0.67		0.74		0.14
Upper respiratory tract infection	9 (15.0%)	9	7 (10.8%)	8	14 (14.7%)	24
Vomiting	8 (13.3%)	11	10 (15.4%)	10	20 (21.1%)	33
Agitation	11 (18.3%)	12	7 (10.8%)	8	8 (8.4%)	10
Headache	8 (13.3%)	8	4 (6.2%)	4	12 (12.6%)	12
Cough	7 (11.7%)	7	5 (7.7%)	5	16 (16.8%)	27
Dyspnea	6 (10.0%)	6	4 (6.2%)	4	10 (10.5%)	10
Rash	3 (5.0%)	3	3 (4.6%)	3	10 (10.5%)	10

Note: PedPRM = pediatric prolonged-release melatonin; TEAE = treatment-emergent adverse event.

<sup>a</sup>Rate = number of observed events for the entire group divided by 13 (double-blind) or 91 (open-label), which equals the number of events for the entire group by week. This value is divided by the number of participants in the group to provide the number of events per week per participant. The value is multiplied by 52 (weeks/year) to determine the number of events per year of treatment per participant.

Source: Malow, BA, RL Findling, CM Schroder, et al., 2021, Sleep, Growth, and Puberty after 2 Years of Prolonged-Release Melatonin in Children with Autism Spectrum Disorder, J Am Acad Child Adolesc Psychiatry, 60(2):252-261 e253

# Clinical Safety – Clinical Trials

## (Melatonin in Children with Autism Spectrum Disorder)

Pubertal Development and Change From Baseline in Mean Standard Deviation Scores at Week 106 in Children  $\geq 8$  Years of Age Treated With Pediatric Prolonged-Release Melatonin (PedPRM)

SDS	PedPRM group				Placebo group			
	Mean (SD)	Range			Mean (SD)	Range		
Pubic hair growth	0.881 (1.11), n = 19	-0.43 to 3.04			1.323 (0.998), n = 12	-0.43 to 2.63		
Breast development	0.709 (1.16), n = 7	-0.12 to 3.14			NA	NA		
Genitalia development	0.692 (0.96), n = 12	-0.55 to 2.12			1.205 (0.8), n = 12	-0.55 to 2.11		
<b>Change from baseline</b>	<b>Mean (SD)</b>	<b>Range</b>	<b>(95%CI)</b>	<b>p</b>	<b>Mean (SD)</b>	<b>Range</b>	<b>(95%CI)</b>	<b>p</b>
Pubic hair growth	1.09 (1.24), n = 16	0.0 to 3.40	(0.49, 1.69)	< .0001	1.55 (1.11), n = 11	0.0 to 2.85	(0.85, 2.35)	< .001
Breast development	1.78 (1.70), n = 5	0.0 to 3.54	(0.21, 3.36)	< .001	NA	NA	NA	NA
Genitalia development	0.74 (1.09), n = 11	0.0 to 2.99	(0.05, 1.43)	< .001	1.30 (1.00), n = 11	0.0 to 2.48	(0.67, 1.94)	< .001

Source: Malow, BA, RL Findling, CM Schroder, et al., 2021, Sleep, Growth, and Puberty after 2 Years of Prolonged-Release Melatonin in Children with Autism Spectrum Disorder, J Am Acad Child Adolesc Psychiatry, 60(2):252-261 e253

## Clinical Safety - Conclusion

- Melatonin appears to be a relatively safe substance for oral administration at the nominators' proposed dose 0.2 mg – 5 mg when used for the short-term treatment of sleep disorders in children and adolescents with autism spectrum disorders
  - Alternative non-pharmacological interventions like cognitive behavioral therapy and behavioral interventions are recommended and may be safer than melatonin for the initial management
- Frequently reported adverse events
  - Somnolence and daytime sleepiness
  - Most adverse events either resolved spontaneously within a few days with no adjustment in melatonin, or immediately upon withdrawal of treatment
- No standard dose recommended for melatonin use in children and there is no information on body weight dosing recommendations

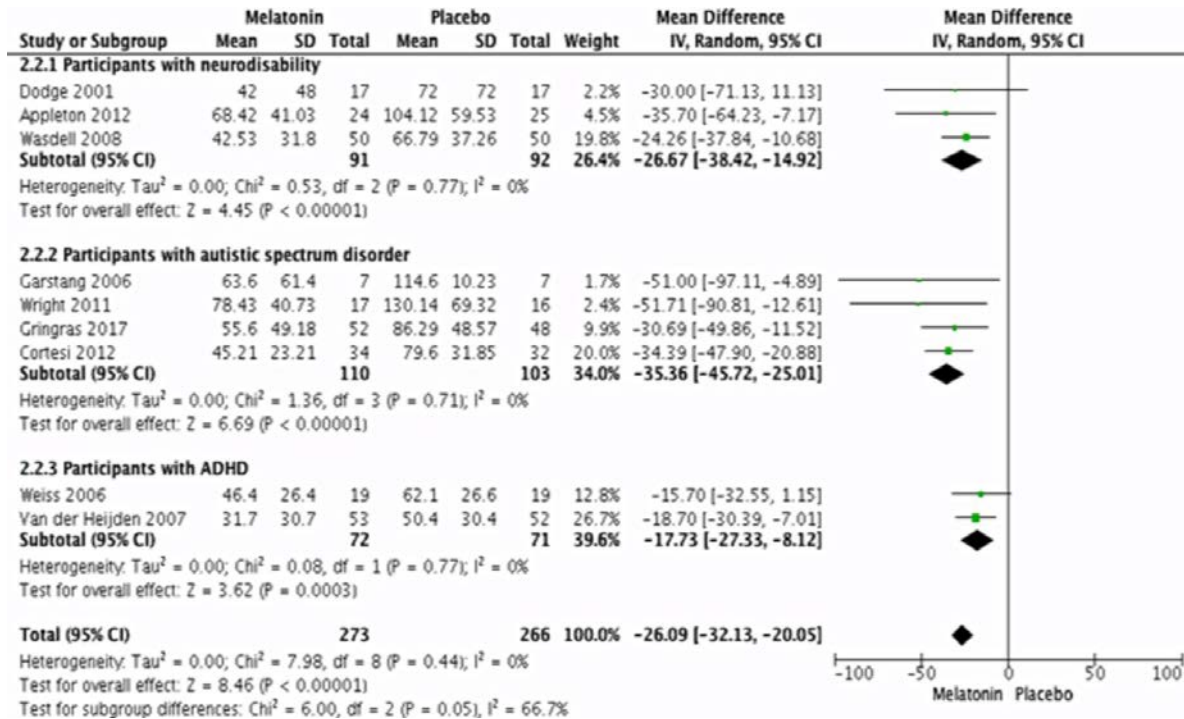
# Sleep Disorder in Autism Spectrum Disorder

- Sleep disorders are more common and severe in children with neurodevelopmental disorders like autism spectrum disorders, compared with typically developing children
  - Between 44% and 83% of children with autism spectrum disorder are reported to experience sleep disorders
- Coexisting sleep disorders can also worsen the core symptoms of autism spectrum disorders
  - Poor sleep quality, and insufficient nighttime sleep can exacerbate cognitive performance deficits, contributing to negative effects on mood, and behavioral problems in addition to negatively affecting sleep and quality of life of the families

# Clinical Effectiveness – Sleep Outcomes

- Sleep onset latency (SOL)
  - Amount of time from lights turned off until the onset of any sleep stage
  - Normal SOL in adults is less than 20 minutes; In children, SOL is 10–26 minutes
  - Prolonged sleep latency would be characterized as difficulty falling asleep
- Night awakenings
  - The number of complete awakenings occurring after sleep initiation
- Total sleep time (TST)
  - Sleep duration during a given sleep period time (usually at night)
  - Reduced TST relates to prolonged SOL, night awakenings, and early-morning waking

# Clinical Effectiveness – Sleep Onset Latency



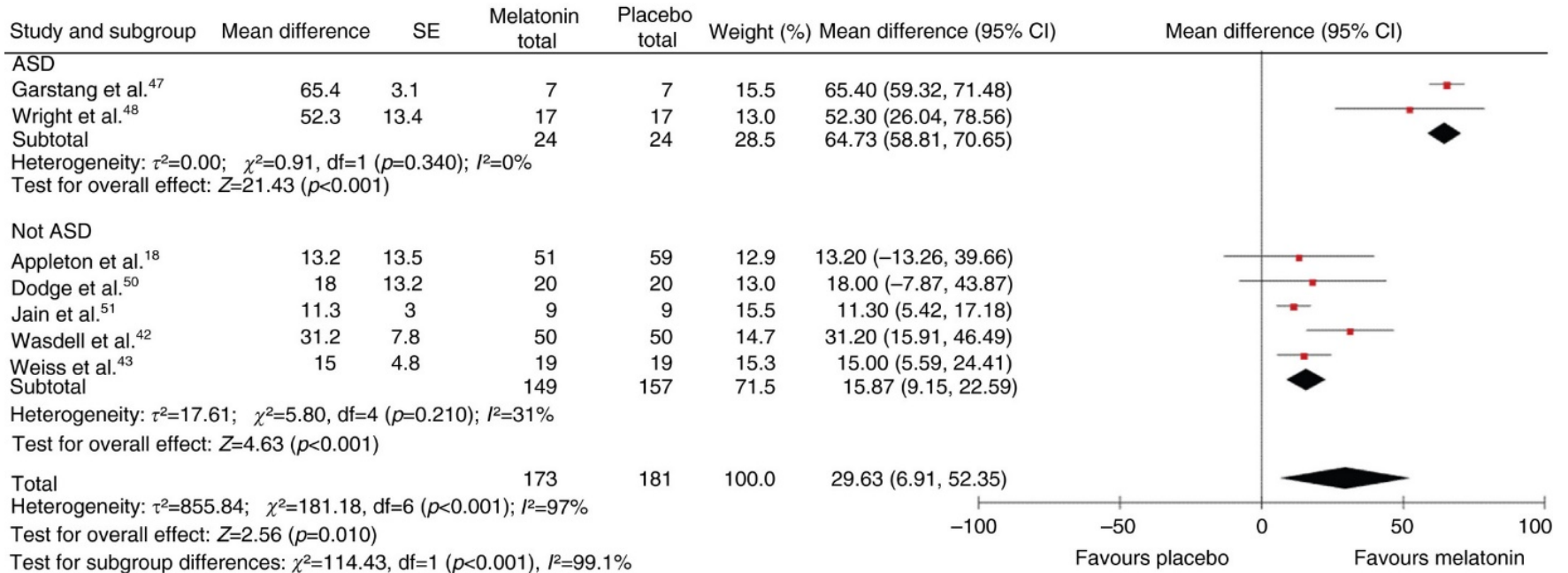
Meta-analysis data from controlled trials that pooled sleep diary-reported sleep onset latency in children with autism spectrum disorder and other neurodevelopmental disorders .

Sleep onset latency defined as the time in minutes from the child being placed in bed to sleep onset. Squares represent the point estimate of the individual study result. The squares also give a representation of the size of the study. Larger squares indicate more participants in the study. SE, standard error; CI, confidence interval; df, degrees of freedom.

Source: Abdelgadir, IS, MA Gordon and AK Akobeng, 2018, Melatonin for the Management of Sleep Problems in Children with Neurodevelopmental Disorders: A Systematic Review and Meta-Analysis, Arch Dis Child, 103(12):1155-1162.



# Clinical Effectiveness – Total Sleep Time



Meta-analysis data from seven controlled trials that pooled sleep diary-reported total sleep time: six crossover trials with a washout period (n=122) and one parallel-group trial (n=110) in children with autism spectrum disorder and other neurodevelopmental disorders.

Squares represent the point estimate of the individual study result. The squares also give a representation of the size of the study. Larger squares indicate more participants in the study. SE, standard error; CI, confidence interval; df, degrees of freedom.

Source: Parker, A, B Beresford, V Dawson, et al., 2019, Oral Melatonin for Non-Respiratory Sleep Disturbance in Children with Neurodisabilities: Systematic Review and Meta-Analyses, Dev Med Child Neurol, 61(8):880-890.

## Clinical Effectiveness – Conclusion

The available evidence suggests that melatonin may be effective for the short-term treatment of sleep disorders in children and adolescents with autism spectrum disorder under the supervision and care of a healthcare practitioner

## Historical Use in Compounding

- Melatonin has been used in pharmacy compounding since at least 2009 and has been compounded in a variety of dosage forms
- According to the Johns Hopkins University Center of Excellence in Regulatory Science and Innovation (JHU CERSI) report, melatonin is sometimes used as a sleep aid in patients with autism spectrum disorder in the U.S.
- Melatonin is approved for use in Europe, Australia, and Japan



## Recommendation

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



**U.S. FOOD & DRUG**  
ADMINISTRATION

# Methylcobalamin

## **Pharmacy Compounding Advisory Committee Meeting** **June 9, 2021**

**Susan Johnson, PharmD, PhD**  
Clinical Reviewer  
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Office of Specialty Medicine  
Office of New Drugs (OND), CDER, FDA



# Methylcobalamin Evaluation Team

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## **Special thanks to the Office of New Drugs:**

Division of Nonmalignant Hematology

Division of Rare Disease and Metabolic Genetics

Division of Psychiatry

Division of Neurology I

Division of Anesthesiology, Addiction Medicine and Pain Medicine



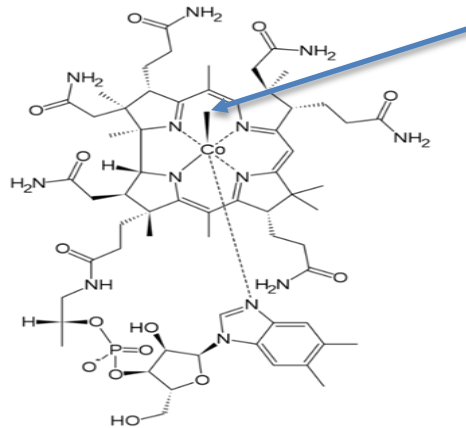
# Nomination

- Methylcobalamin has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug and Cosmetic Act (FD&C Act).
- It was reviewed for use in the treatment of vitamin B<sub>12</sub> deficiency, various inborn errors of metabolism, hyperhomocysteinemia, autism spectrum disorder (ASD), amyotrophic lateral sclerosis (ALS), peripheral neuropathies and pain conditions.
- The proposed dosage forms include oral, sublingual, nasal spray and injectable solution for subcutaneous or infusion administration.



# Physical and Chemical Characterization

- Vitamin B<sub>12</sub> is comprised of 4 structurally related substances (vitamers)
- Methylcobalamin and the other vitamers have well characterized structures (Ganesan et al. 2012)
  - Base is a cobalamin molecule
  - Each vitamer has a different ligand
  - Substances are called “cobalamins”



Ligand changes at this position form different cobalamins:

CH<sub>3</sub>, as shown - methylcobalamin

OH - hydroxocobalamin

CN - cyanocobalamin

5' deoxyadenosyl - adenosylcobalamin

# Physical and Chemical Characterization (2)

	Naturally occurring in humans	Naturally occurring in food sources	Component of FDA approved products	Marketed as dietary supplement (oral)*
Methylcobalamin	Yes	Meat, fish, fowl, milk, eggs	No	Yes
Adenosylcobalamin	Yes	Meat, fish, fowl, milk, eggs	No	Yes
Hydroxocobalamin	No	(No)	Yes (intramuscular injection; intravenous infusion for cyanide poisoning only)	Yes
Cyanocobalamin	No (can be seen at low levels in smokers)	No	Yes (intramuscular or subcutaneous injection; nasal spray)	Yes

\* The availability of a substance as a dietary supplement is **not** a criterion considered when evaluating a substance for inclusion on the 503A Bulks List. 84 FR 4702. This presentation focuses on FDA's evaluation of methylcobalamin as a bulk drug substance for use in human drug compounding under section 503A and is not intended to inform FDA's regulation of methylcobalamin in dietary supplements.

## Physical and Chemical Characterization (3)

- Methylcobalamin is stable at room temperature in solid formulations when protected from light
- As an aqueous solution it is stable when protected from light and stored at a controlled temperature with a controlled pH
- The bulk drug substance (BDS) is synthesized via methylation of hydroxocobalamin; impurities are unlikely to be toxic

### **Conclusion:**

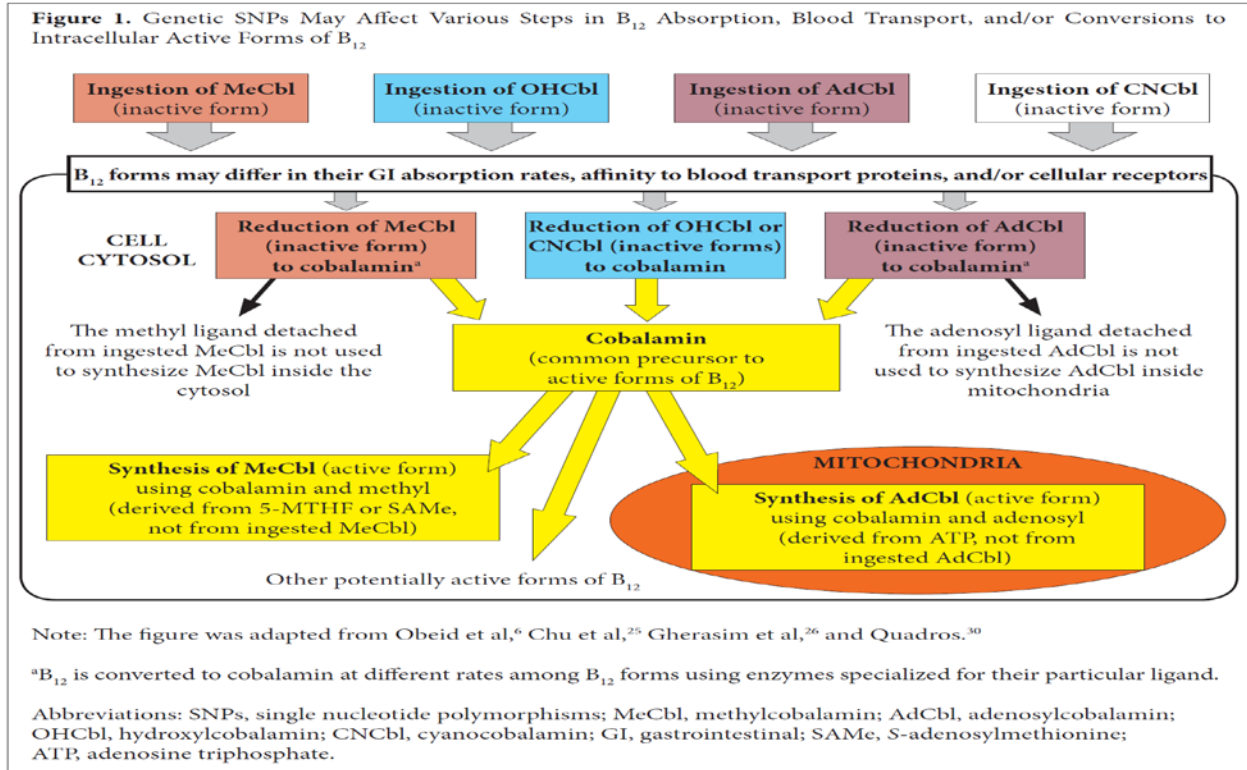
Methylcobalamin is well characterized.

It is likely to be stable in solid and liquid dosage forms provided that it is protected from light. As a solution, controlled temperature and pH are also required for stability.

# General Pharmacology

- Gastrointestinal absorption (Allen et al. 2018)
  - Once ingested, cobalamins are dissociated from food protein at the low pH of the stomach; cobalamins are bound to haptocorrin
  - At the higher pH of the duodenum and ileum, cobalamins dissociate from haptocorrin and are bound to intrinsic factor
  - A receptor-mediated calcium dependent endocytosis moves the intrinsic factor-cobalamin complex into ileal enterocytes
  - Cobalamin is released from intrinsic factor to bind to unsaturated transcobalamin or haptocorrin
  - Passive absorption throughout the gastrointestinal tract allows for absorption without the intrinsic factor pathway and likely accounts for absorption in the nose and mouth
  
- Transport in plasma (Paul and Brady 2017)
  - Cobalamins are transported through the plasma bound to transcobalamin or haptocorrin to the liver or other cells
  - Cobalamins are not active during absorption and transport

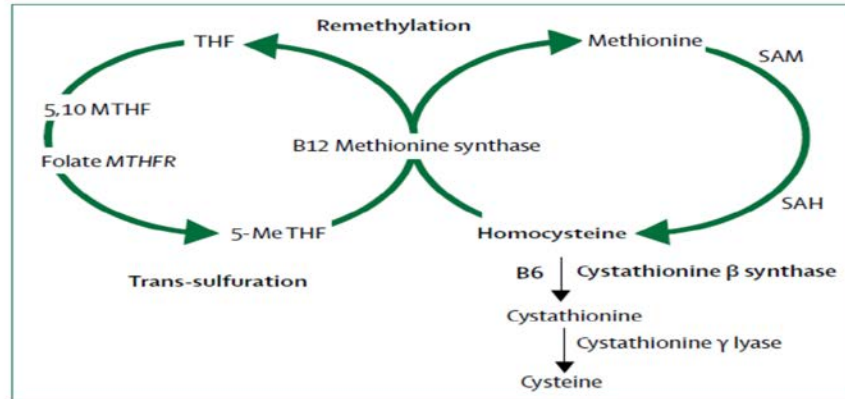
# General Pharmacology (2)



Source: Paul and Brady 2017

# General Pharmacology (3)

- Once activated, methylcobalamin acts in the cell cytosol (Spence et al. 2017)
  - Methylcobalamin is a cofactor for methionine synthase in the folate-dependent reaction that converts homocysteine to methionine
  - Methionine is required for protein synthesis and for synthesis of S-adenosylmethionine (SAM), a methyl group donor in the synthesis of DNA, RNA, proteins and lipids



**Figure 1: Homocysteine metabolism**  
 B12=cobalamin. B6=pyridoxine. MTH=methylenetetrahydrofolate.  
 MTHFR=methylenetetrahydrofolate reductase. SAM=S-adenosylmethionine.  
 SAH=S-adenosylhomocysteine. 5-Me THF=5-methyl tetrahydrofolate.

# Nonclinical Pharmacokinetics and Safety

- Oral dosing in rodents showed that, in general, the pharmacokinetics for cobalamins have similarities (Tsukerman et al. 1992):
  - Low bioavailability with saturable absorption kinetics
  - Accumulation in the liver
  - Excretion mainly in the urine
  
- Acute toxicity studies in several species showed that methylcobalamin is safe to be given by oral and parenteral routes at high doses for short periods of time (anonymous, Kiso to Rinsho 1970). Intravenous administration was associated with an LD<sub>50</sub> of:
  - > 5 g / kg in rats and mice
  - > 200 mg / kg in dogs
  - > 75 mg / kg in rabbits
  
- Studies of repeat dose toxicity, genotoxicity, developmental and reproductive toxicity and 2 year (life span) carcinogenicity were not found in the published literature

# Clinical Pharmacokinetics

- We found limited clinical pharmacokinetic data for methylcobalamin
- The European Food Safety Authority (EFSA 2000) proposed that 500 mcg is the appropriate daily dose for methylcobalamin or adenosylcobalamin for adults
- Clinical studies have shown:
  - Methylcobalamin and cyanocobalamin have similar absorption profiles (Adams et al. 1971)
  - Oral bioavailability of cobalamins is inversely proportional to the consumed dose, likely due to the saturation of receptors that mediate ileal absorption
  - Much of absorbed cobalamin is excreted in the bile, but some is reabsorbed in the ileum due to enterohepatic circulation
  - A small amount (several milligrams) of cobalamin is normally stored in the liver, but that amount can be increased following supplemental administration of cobalamins
  - Only 0.1 – 0.2% of cobalamin is lost per day due to metabolic activity and is excreted in primarily in the urine (European Commission Scientific Committee on Food 2000)



# Clinical Safety

- No published safety studies of methylcobalamin were found
- Some studies of clinical use of methylcobalamin provided adverse event data. For example,
  - ASD studies reported hyperactivity, reduced sleep “mouthing of objects,” increased irritability, nosebleeds and cold/flu/fever symptoms
  - Flushing and injection site reactions were reported in other studies
- FDA approved labeling of hydroxocobalamin and cyanocobalamin products include safety information that may be relevant to use of methylcobalamin due to apparent similarities in pharmacologic activity. For example,
  - Hypokalemia and sudden death due to intense treatment of megaloblastic anemia;
  - Hypersensitivity, anaphylactic shock and death
  - Most common adverse reactions (> 5%) include transient chromaturia, erythema, oxalate crystals in the urine, rash, increased blood pressure, nausea, headache and infusion site reactions.

## Clinical Safety (2)

- FDA Adverse Event Reporting System (FAERS)
  - 174 serious reports with methylcobalamin use
  - 22 U.S. and 152 foreign reports
  - One death was reported among the foreign reports of a 21 year old female who had taken methylcobalamin during treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis; it was unlikely due to methylcobalamin
  - Two U.S. cases reported use of methylcobalamin alone and were considered assessable

Case #1 – a 38 year old male with multiple sclerosis reported that several months after initial dosing with 5,000 mcg per week divided into 4 intramuscular doses, he developed severe cramps and numbness in one leg. Months later, he experienced dizziness, fatigue, shortness of breath and increased numbness. His physician reduced his dose to 2,000 mcg per week and symptoms subsided. He also noted having received an expired vial of methylcobalamin from his compounding pharmacy.

Case #2 - The mother of a 3 year old girl reported that her daughter experienced increased liver enzymes and yellowing of hands and feet after receiving methylcobalamin shots for methionine synthetase deficiency for 3 months. No additional information was provided.

## Clinical Safety (3)

- The Center for Food Safety and Nutrition (CFSAN)'s Adverse Event Reporting System (CAERS) included:
  - 384 reports that mention methylcobalamin use
  - Most reports describe use of products with multiple ingredients and/or use of multiple products such that the relationship to methylcobalamin use is confounded
  - Six deaths were reported but none of the reports have sufficient information to assess causality
  - Two reports describe events associated with use of a methylcobalamin only product

Report #1 - One “customer” reported being hospitalized for anxiety but did not know if there was a relationship to methylcobalamin.

Report #2 - A 75 year old man reported having taken the product for two days when he began to feel dizzy and to eat poorly. He was seen in an emergency department, found to be dehydrated, given fluids and recovered.

# Safety Conclusion

- Methylcobalamin is found in foods and oral use of methylcobalamin as a dietary supplement does not appear to be associated with serious adverse events
- Overall, we have sufficient data to characterize the safety of FDA approved cobalamin products
  - Based on the likely comparability of the mechanism of action of methylcobalamin to cyanocobalamin and hydroxocobalamin, and the listing of serious events in their FDA approved labeling, serious adverse effects could occur with methylcobalamin use
  - No studies were found that compared the safety of the various cobalamin substances
- We have a concern regarding lack of available safety data, particularly of intravenous injections and infusions, used for a variety of conditions, some of which are serious
  - Specific information supporting the safety of injectable methylcobalamin could not be found

# Effectiveness – Vitamin B<sub>12</sub> Deficiency

- Vitamin B<sub>12</sub> deficiency (Allen et al. 2018; Stabler 2013)
  - Defined as a serum level of B<sub>12</sub> less than 111 – 148 pmol/L, depending on organization
  - Can be associated with vegetarian or vegan diets
  - Has a prevalence of approximately 5% of persons age 60 and older in U.S., commonly due to chronic autoimmune gastritis targeting parietal cells or intrinsic factor
  - Can cause pernicious anemia
  - Is typically treated in the U.S. with 1000 mcg hydroxocobalamin or cyanocobalamin given as intramuscular injections for 1 - 2 weeks, then weekly. This may be followed by use of high dose oral administration
- An observational study of 28 children in New Delhi (Verma et al. 2017)
  - One month of treatment with oral methylcobalamin at doses of 30 mcg/kg/day
  - Treatment corrected low holotranscobalamin (cobalamin in the serum bound to transcobalamin) levels in 27 of the children
- Other studies have been described with little detail

## Effectiveness – Vitamin B<sub>12</sub> Deficiency (2)

### Conclusions:

- The pharmacologic mechanism of methylcobalamin suggests that it is likely to be effective in treating vitamin B<sub>12</sub> deficiency
- Some clinical evidence of effectiveness was found from outside the U.S., where methylcobalamin is more commonly used than the FDA approved cobalamin products
- No U.S. studies were found of methylcobalamin in the treatment of vitamin B<sub>12</sub> deficiency, nor any studies comparing methylcobalamin to other cobalamins for treatment of vitamin B<sub>12</sub> deficiency
- No data were found that show hydroxocobalamin or cyanocobalamin are insufficient to provide treatment for vitamin B<sub>12</sub> deficiency

# Effectiveness – Inborn Errors of Metabolism



- Inborn errors of metabolism include rare diseases that can affect various aspects of the absorption, transport in the blood, intracellular metabolism or physiologic action of cobalamins
  - The specific inborn error determines whether the condition is responsive to supplemental cobalamin use (Hermann and Obeid 2012)
  - In the U.S., cobalamin-responsive diseases are treated with chronic, supplemental hydroxocobalamin or cyanocobalamin (Huemer and Baumgartner 2019)
  - No studies of the use of methylcobalamin in these diseases have been found

# Effectiveness – Inborn Errors of Metabolism (2)



- Methylene-tetrahydrofolate reductase (MTHFR) deficiency and MTHF dehydrogenase (MTHFD1) deficiency (Huemer et al. 2017)
  - Caused by inborn errors of metabolism within the folate cycle
  - Result in homocysteinuria and are treated with folic acid and betaine
  - No studies of the use of methylcobalamin to treat these diseases has been found
  - These conditions are distinct from polymorphisms of the MTHFR gene, which have unclear clinical consequences
- Classic homocystinuria (cystathione beta synthase deficiency)
  - Inborn error of metabolism that reduces homocysteine metabolism to cysteine
  - Treated in the U.S. with hydroxocobalamin
  - No studies of the use of methylcobalamin were found

**Conclusion:** No clinical studies were found that support the effectiveness of methylcobalamin to treat inborn errors of metabolism.



# Effectiveness – Hyperhomocysteinemia

- This condition is not an inborn error of metabolism
  - It is classified as moderate (15 to 30  $\mu\text{mol/L}$ ), intermediate (30 to 100  $\mu\text{mol/L}$ ) or severe (greater than 100  $\mu\text{mol/L}$ ) (Lonn 2006)
- It can be caused by hypothyroidism, certain malignant tumors, pernicious anemia, sickle cell anemia and certain drugs, such as metformin
- 85% of patients with chronic kidney disease (CKD) also have hyperhomocysteinemia
- Folic acid has been used to lower homocysteine levels, but this has not been found to reduce risk of mortality or cardiovascular events (de Koning and Hu 2010; Cianciolo et al. 2017)
- The National Kidney Foundation’s 2020 Clinical Practice Guidelines for Nutrition in CKD does not recommend routine use of folate, vitamin B<sub>12</sub> or B-complex except to correct for deficiency/insufficiency

**Conclusion:** No specific data were identified to support the effectiveness of methylcobalamin in the treatment of hyperhomocysteinemia.



# Effectiveness – Autism Spectrum Disorder (ASD)

- Uncontrolled, open-label study of children age 2 to 7 years with “autistic disorder” (James et al. 2009)
  - Treated for 3 months with both 75 mcg/kg of methylcobalamin twice weekly via subcutaneous injection and 400 mcg folinic acid twice a day; 40 children completed the study
  - Scores on Vineland Adaptive Behavioral Scale (VABS) were reported to have significantly improved but were not published
- Uncontrolled, open-label study of 44 children with a mean age of 5 years with “autistic disorder” (Frye et al. 2013)
  - Treated for 3 months with both 75 mcg/kg twice weekly subcutaneously and 400 mcg of folinic acid twice daily
  - VABS score improved in 37 patients who completed the study; interpretation is unclear without placebo comparator
  - Authors confirm need for double blind, placebo-controlled, large-scale multicenter studies

## Effectiveness – ASD (2)

- Double-blind, placebo-controlled crossover study of 30 children with autism age 3 to 8 (Bertoglio et al. 2010)
  - 6 week treatment with 64.5 mcg/kg of methylcobalamin subcutaneously or placebo every 3 days, then alternative
  - No statistically significant differences between groups were found on the Clinical Global Impression-Improvement (CGI-I) Scale or 5 other behavioral assessment scales
  
- Double-blind, placebo-controlled study in 57 children age 3 to 7 with ASD (Hendren et al. 2016)
  - Treated for 8 weeks with 75 mcg/kg subcutaneous methylcobalamin or placebo every 3 days
  - Within group improvement on CGI-I was statistically higher for methylcobalamin group than for placebo.
  - No difference on two other behavioral scales assessing specific ASD symptoms.

## Effectiveness – ASD (3)

- Johns Hopkins University Center for Excellence in Regulatory Science and Innovation (JHU CERSI)
  - Conducted an “Evaluation of Bulk Drug Substances Used to Compound Drug Products for Patients with Autism Spectrum Disorder”
  - 3 Key Opinion Leaders, clinical experts in autism, found that “B12 would likely have no effect (in autism) unless specifically taken to address a dietary deficiency”

**Conclusion:** Available data do not support the effectiveness of methylcobalamin in treating ASD.

## Effectiveness – Amyotateral Sclerosis (ALS)

- The outcome of a Phase II/III study conducted in Japan (ClinicalTrials.gov ID: NCT0044613) was reported in 2018.
  - Doses of 25 or 50 mg methylcobalamin, or placebo, were given by intramuscular injection twice a week over 3.5 years in 373 patients
  - Primary analyses showed no differences between treatment groups
  - In a post-hoc analysis, patients who had been enrolled within one year of ALS diagnosis were found to have improved survival
- Based on this finding, it was reported in 2019 that a second, similar trial was being conducted in Japan
  - Although results were expected to have been published in March 2020, no related information has been found

**Conclusion:** We were unable to identify any studies that show methylcobalamin is effective in the treatment of ALS.

# Effectiveness – Peripheral Neuropathy

- Diabetic peripheral neuropathy
  - One study of 50 patients who received 500 mg methylcobalamin or placebo 3 times daily for 4 months (Yaqub et al. 1992)
  - Peripheral neuropathy assessment scale was analyzed only for within group changes
  - Not a recommendation in the American Diabetes Association Standards of Medical Care in Diabetes 2021
- Uremic-diabetic polyneuropathy (Kuwabara et al. 1999)
  - One uncontrolled study in which 9 patients receiving maintenance hemodialysis were given 500 mcg 3 times a week for 6 months
  - Numerical decline in average neuropathic pain score (1.8 to 1.4 on 0 to 3 scale)
  - Authors confirm that placebo effect could account for changes
- Chemotherapy-induced peripheral neuropathy
  - One randomized, placebo-controlled study with 47 patients' results analyzed (Schloss et al. 2017)
  - No statistically significant differences on a neurologist assessed total neuropathy score
- Chronic idiopathic axonal polyneuropathy (CIAP) – no studies were found

**Conclusion:** Available data do not support the effectiveness of methylcobalamin in treating peripheral neuropathy

## Effectiveness – Pain

- Herpetic neuralgia (Xu et al. 2013)
  - Active control study of 98 patients received local subcutaneous injection of methylcobalamin, oral methylcobalamin or local subcutaneous lidocaine 1%
  - Numerical trends on pain rating favored methylcobalamin injection without placebo comparison
  - Authors confirm need to replicate findings
- Lumbar spine stenosis (Waikakul and Waikakul 2000)
  - 152 patients received standard care (oral analgesics, physiotherapy, etc.) with or without 500 mcg oral methylcobalamin 3 times a day for 6 months
  - No statistical differences between groups on pain or other neurological findings
- Low back pain (Chiu et al. 2011)
  - Randomized, double-blind, placebo-controlled trial of 60 patients
  - 6 intramuscular injections of 1000 mcg methylcobalamin or placebo over 6 weeks.
  - Within group changes were reported on disability index and pain visual analog

**Conclusion:** Available data do not support the effectiveness of methylcobalamin in treating pain.



## Effectiveness - Conclusion

- The pharmacologic mechanism of methylcobalamin suggests that, like FDA approved cobalamin products, it is likely to be effective in treating vitamin B<sub>12</sub> deficiency.
  - We found no data regarding clinical situations in which FDA approved hydroxocobalamin or cyanocobalamin products are insufficient to provide treatment
- We found negligible or no specific information that supports the effectiveness of methylcobalamin to treat inborn errors of metabolism, hyperhomocysteinemia, ASD, ALS, peripheral neuropathy, or pain



# Historical Use in Compounding

- FDA requested current and historical use information from the University of Maryland Center of Excellence in Regulatory Science and Innovation (UMD CERSI)
  - No compounded drug products containing methylcobalamin were identified in the literature review
  - Methylcobalamin is most commonly used to treat diabetic peripheral neuropathy and hyperhomocysteinemia.
  - In a survey of 27 practitioners, 5 reported having used, prescribed or recommended compounded methylcobalamin. This survey was limited by sample size and potentially by self-reporting bias.
- Johns Hopkins University (JHU) CERSI evaluated the use of six bulk drug substances in ASD
  - In a clinical sample of 1,788 ASD patients under 17 years of age at the Kennedy Krieger Institute Center for Autism and Related Disorders < 1% of children received oral vitamin B<sub>12</sub>
  - In a population sample of 1,487 parents of children under 18 years of age with autism, an online registry showed 6% used methylcobalamin and 5.5% used “B complex,” usually in oral form
  - In a national sample of Medicaid claims for 2010 – 2014, vitamin B<sub>12</sub> was reported to have been used in 1.1% of ASD patients and approximately the same portion of children without ASD.

# Historical Use in Compounding

- Published references to methylcobalamin compounding since 2005
- The International Journal of Pharmaceutical Compounding has published compounding formulations for sublingual troche and liquids, and intramuscular injections
- Methylcobalamin is not found in the British or European pharmacopoeias
  - It is approved in Japan, China, Hong Kong and Australia.
- Online promotions for compounding pharmacies and treatment clinics in the U.S. were found to promote use of methylcobalamin in a wide variety of conditions and diseases
  - Use of various dosage forms including oral, sublingual, nasal and oral spray, intramuscular and subcutaneous injections, intravenous infusions are promoted.

**Conclusion:** Methylcobalamin is promoted in the U.S. to treat a wide variety of conditions in various dosage forms, including intravenous infusions. The JHU CERSI report found that it is not widely used to treat ASD.

# Effectiveness, Use and Safety Considerations

- Effectiveness
  - Methylcobalamin is a vitamer of vitamin B<sub>12</sub>
  - Based on the use of the other cobalamins, methylcobalamin would be expected to be effective in treating vitamin B<sub>12</sub> deficiency.
  - It is unclear that methylcobalamin provides a unique benefit over the other vitamers of B<sub>12</sub> that are available in FDA approved drug products
- Use
  - It is not clear that the treatment of vitamin B<sub>12</sub> deficiency is currently the primary use of compounded methylcobalamin in the U.S.
  - It appears that the primary use of compounded methylcobalamin is to treat patients with conditions, in some cases serious, for which there is little evidence to support the effectiveness.
- Safety
  - We do not have information on the range of doses or the frequency of administration
  - We cannot make a judgement on the safety of the current use of injectable products in patients.



## Recommendation

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



**U.S. FOOD & DRUG**  
ADMINISTRATION



# Choline Chloride

## Pharmacy Compounding Advisory Committee Meeting June 9, 2021

Suhail Kasim, MD, MPH  
Lead Physician  
Pharmacy Compounding Review Team  
Office of Specialty Medicine  
Office of New Drugs (OND), CDER, FDA



# Choline Chloride Evaluation Team

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## **Special thanks to the Office of New Drugs:**

Division Of Hepatology and Nutrition

Division of Division of Diabetes, Lipid Disorders & Obesity

Division of Neurology

# Nomination

- Choline chloride has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
- Choline chloride was proposed for use with respect to:
  - liver diseases (including nonalcoholic fatty liver disease), hepatic steatosis, fetal alcohol spectrum disorder, and atherosclerosis
- FDA has opted to evaluate choline chloride for the unnominated use of supplementation in long term total parenteral nutrition
- Proposed routes of administration
  - Parenteral injection route (50 mg/ml as a chloride salt) as slow intravenous and intramuscular preparations



# Physical and Chemical Characterization

- Small, endogenous molecule
- Soluble in water
- Synthesis involves the reaction between trimethylamine and ethylene epoxide in the presence of hydrochloric acid
- It is stable under ordinary storage conditions for up to one year, and is likely to be stable when compounded in solutions for injection

**Conclusion:** Choline Chloride is well characterized physically and chemically and is likely to be stable under ordinary storage conditions in the proposed dosage form

# General Pharmacology



- Choline was officially recognized as an essential nutrient by the Institute of Medicine in 1998
- About half of the dietary choline is in the form of phosphatidylcholine
- Endogenously produced via *de novo* synthesis in the liver by methylation of phosphatidylethanolamine
- Following intestinal absorption choline is stored in the liver and ultimately metabolized in the liver



# Nonclinical Safety

- Acute toxicity
  - No toxicity was observed up to 6 g/kg oral exposure in rodents. Overall, a low toxicity profile using various routes of administration in rodent models was observed.
- Repeat dose toxicity
  - 8-month intraperitoneal study in rats (148.5 mg/kg/day, 5 times weekly for 3 or 6 months)
    - Lung abnormalities
      - 3 months - Lymphoid cells found around bronchioles and abnormal lymphatic vessels
      - 6 months - Giant cells in the alveolar lumen along with fibrosis
    - Liver abnormalities
      - 3 months - No major changes were seen
      - 6 months - Necrosis with increased lymphocytes in the portal area, and granulomas containing mononuclear cells

# Nonclinical Safety (2)



- Genotoxicity
  - Choline chloride was not genotoxic in a standard panel of genotoxicity assays
- Developmental and reproductive toxicity
  - Transient effect on spermatogonia in male rats exposed for up to 24 days to 80 mg/kg/day via intraperitoneal (IP) administration. Changes were reversed by day 12 of the study
  - No data on fertility effects reported in females
  - Embryo-fetal studies in mice showed maternal toxicity (decreased maternal body weight at >1250 mg/kg/day) and increased fetal mortality at >1250 mg/kg/day
- Carcinogenicity
  - Long term (2-year) carcinogenicity studies have not been conducted

## (FDA Adverse Event Reporting System FAERS)

- The following cases were confounded by the use of multiple medications or multi-ingredient products that included choline chloride as one of the ingredients
  - Two cases involved gastrointestinal adverse events (diarrhea and vomiting) after a weight loss injection containing multiple substances including choline chloride was administered
  - Two cases involved injection site adverse events (injection site pain, injection site mass, and injection site hypoesthesia)
  - One case involved a drug hypersensitivity adverse event after taking choline chloride via an unknown route, when administered in addition to 12 other medications
  - One case involved increased blood pressure, headache, anxiety, and restlessness after taking “skinny shots” (for weight loss) containing choline, inositol, and methionine, in addition to oral naltrexone/bupropion (Contrave)

Conclusion: It is difficult to assess causality due to the multiple ingredients used at the time of the adverse events

## (CFSAN Adverse Event Reporting System CAERS)

- Verve Energy Supplement (two cases)
  - Vomiting, nephrolithiasis, increased body temperature; seen in the ER
  - Hypertension, increased heart rate; seen in the ER
- Clear Muscle Performance products (three cases)
  - Cardiac fibrillation, hyperhidrosis, increased heart rate. Resolved spontaneously; no medical intervention reported
  - Choking episode using the product; hospitalized
  - Asthma exacerbation

Conclusion: Insufficient information was provided to interpret the contribution of choline chloride. Considering that there were many other substances in the dietary supplement, it was not possible to determine whether a causal connection existed between choline chloride and the adverse events reported

# Clinical Safety (Clinical Studies)



- Mild nausea, headache, and perspiration
  - plasma-free choline concentrations greater than 200 nmol/ml (normal 10 – 15 nmol/ml)
- Fishy body odor, sweating, diarrhea, salivation, and hypotension (Food and Nutrition Board, Institute of Medicine 1998)
  - In patients with tardive dyskinesia and cerebellar ataxia, doses of 10 and 16 grams/day (dosage form or route of administration not specified) administered for 2 to 6 weeks, were associated with fishy body odor, vomiting, salivation, sweating, and gastrointestinal effects
- Hypotension
  - Daily oral administration of 10 g choline chloride (7.5 g choline) in patients with Alzheimer's disease had a slight hypotensive effect

**Conclusion:** In most clinical studies, choline has been found to be well tolerated and not associated with significant adverse events

# Hepatic Steatosis

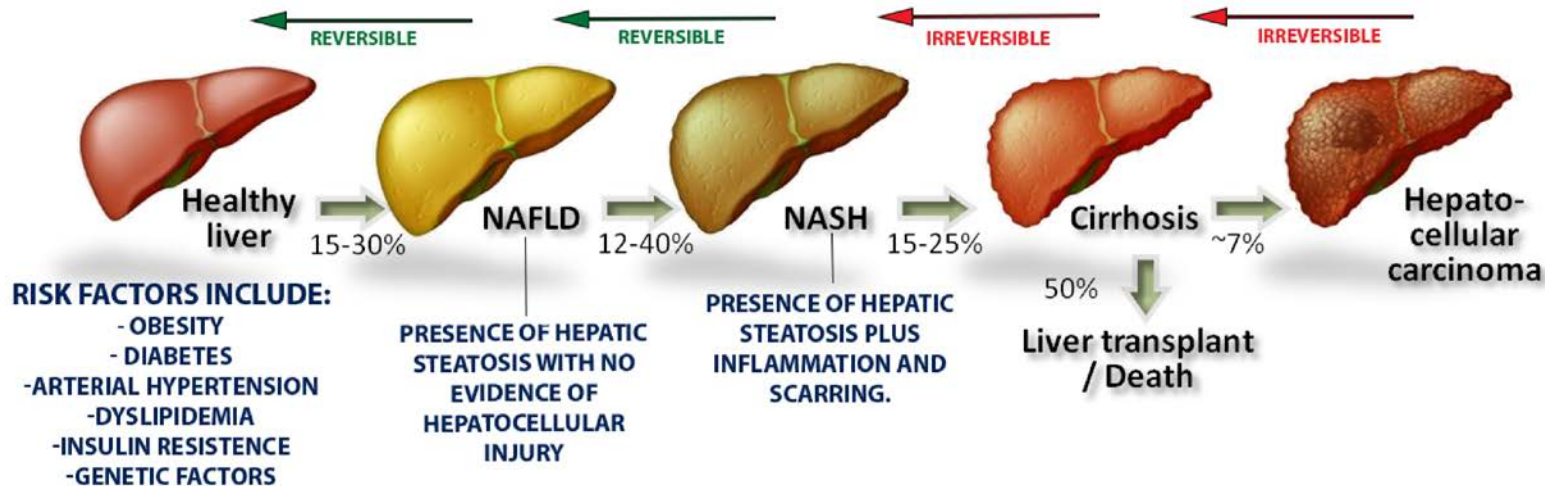
- Characterized morphologically by microvesicular or macrovesicular intracellular lipid formation
  - Hepatic steatosis or fatty liver is defined as intrahepatic triglycerides of at least 5% of liver weight or 5% of hepatocytes containing lipid vacuoles. Causes include alcohol ingestion, drugs, viral infection, obesity, insulin resistance, hyperglycemia, high cholesterol, and elevated triglycerides
  - This finding of hepatic steatosis is a benign condition
  - In rare instances over many years to several decades, there may be increased triglyceride accumulation with progression to more severe chronic liver disease



# Non-Alcoholic Fatty Liver Disease (NAFLD)

- Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of histological changes
  - NAFL - simple fatty infiltration of the liver, also known as simple or isolated (*hepatic*) steatosis or nonalcoholic fatty liver
  - NASH - nonalcoholic steatohepatitis is an extreme form of NAFLD and is regarded as a leading cause of cirrhosis in the United States
  - Associated conditions with NAFLD include obesity, type 2 diabetes mellitus, dyslipidemia (e.g., ↑ triglycerides). The common finding in all these metabolic abnormalities is insulin resistance
  - The risk of development of cirrhosis in patients with simple fatty liver disease is 0.5% to 1%
- At present, clinicians cannot predict which patients are likely to progress from benign steatosis to steatohepatitis, cirrhosis, or end-stage liver disease

# Hepatic Steatosis and Non-Alcoholic Fatty Liver Disease (NAFLD) Spectrum



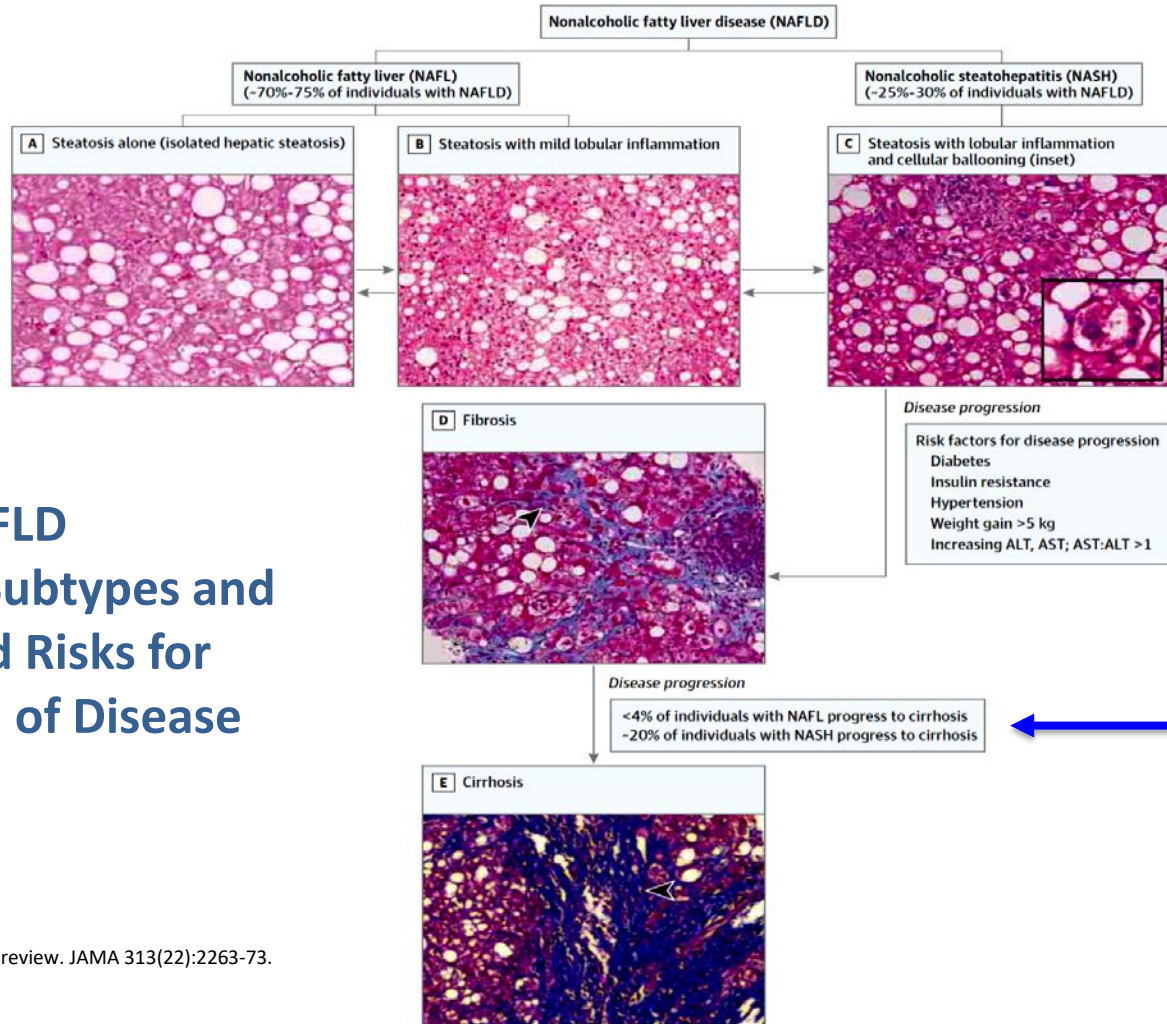
Source: Texas Liver Institute. <https://txliver.com/patient-education/fatty-liver-2/>. Accessed on May 20, 2021

**Conclusion:** Hepatic steatosis is not specific to a disease condition

- It is a *histological finding*
- Typically, hepatic steatosis is transient and reversible. Most humans who have evidence of hepatic steatosis are not adversely affected by its presence

# NAFLD

## Histological Subtypes and Associated Risks for Progression of Disease



Source: Rinella ME.2015.  
 Nonalcoholic fatty liver disease: a systematic review. JAMA 313(22):2263-73.

## Choline - Hepatic Steatosis and NAFLD

- Theoretically, individuals who were to consume a *diet deficient in choline*, can develop hepatic steatosis and go on to develop liver damage (NAFLD)
- The lack of dietary sources of *phosphatidylcholine* limits the export of excess triglyceride from liver in lipoproteins
  - This fat accumulation within the hepatocytes predominantly in the form of triglycerides can result in the NAFLD disease spectrum that includes histological evidence of hepatic steatosis
- Patients are unlikely to develop hepatic steatosis with an adequate dietary choline. *The US diet is rich in choline-containing foods*
- Patients on long-term parenteral nutrition (PN) that lack adequate choline in the form of phosphatidylcholine and phosphatidylethanolamine can develop steatosis

# Clinical Effectiveness

## Treatment of Liver Diseases (including NAFLD)

- Six practice guidelines pertain to the treatment of NAFLD
  - Choline chloride is not recommended for NAFLD in any of the treatment guidelines<sup>1</sup>
  - We could not find clinical evidence that choline chloride administration will be effective in the treatment of NAFLD that is not related to a deficiency of choline
- Three studies related to choline in liver disease are summarized

<sup>1</sup> Chalasani et al. 2012; Cotrim et al. 2016; European Association for the Study of the Liver, 2016; National Institute for Health and Care Excellence 2016; Vos et al. 2017; Chalasani et al. 2018

## Clinical Effectiveness NAFLD (Study 1)

- Forty-three children and adolescents aged 4-16 years with baseline liver biopsy confirming NASH were studied. (Zohrer et al. 2017)
- Pro DHA Steatolip Plus (Choline 201 mg, Docosahexaenoic acid (DHA) 250 mg, vitamin E 39 IU) or placebo were administered PO for 6 months
- Primary outcome measure: improvement in liver hyperechogenicity by ultrasound (US) at 12 months of treatment
- Primary outcome (subgroup analysis): Decrease in severe steatosis

## Clinical Effectiveness NAFLD (Study 1) (2)

- No between treatment comparison; only change from baseline within group analysis

%	Placebo			DHA-CHO-VE		
	Baseline	12 mo	<i>p</i>	Baseline	12 mo	<i>p</i>
No steatosis	0	0	—	0	35	—
Mild	25	45	0.18	15	35	0.14
Moderate	40	45	0.75	40	25	0.31
Severe	35	15	0.14	50	5	0.001*

**Note:** DHA-CHO-VE, docosahexaenoic acid, choline, and vitamin E.

\* $\chi^2$  test,  $p < 0.05$  was considered significant.

- Multiple ingredients in treatment prevent attributing any benefit to choline

## Clinical Effectiveness NAFLD (Study 2)

- Study sought to determine whether subjects with biopsy proven NAFLD and evidence of an inadequate intake of choline had more severe histological features on biopsy compared to subjects with adequate choline intake (Guerrero, et al. 2012)
- Subjects were enrolled in the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN)
- Amount of choline in diet estimated from food questionnaire within 6 months of liver biopsy; biopsies scored centrally with NASH CRN scoring system
- Choline deficiency was not identified as a contributor to liver disease severity in three cohorts: children (n=114), men (n=240), or premenopausal women (n=116)
- Postmenopausal women (n=194) with a diet deficient in choline had increased fibrosis
- No intervention to determine whether liver disease improves with choline treatment



## Clinical Effectiveness NAFLD (Study 3)

- Twenty patients with cirrhosis treated with 1.5 to 3 grams of choline and cystine for one to five months compared to 15 control patients (Beams 1946)
- Difficult to follow the conduct of the study, the range of severity of disease in patients enrolled, and underlying etiology of cirrhosis
- Effectiveness endpoints are poorly defined
- Study provides no evidence of effectiveness of choline in chronic liver disease and cirrhosis

# Clinical Effectiveness

## Long Term Total Parenteral Nutrition

- Choline deficiency can occur in long-term total parenteral nutrition patients that are not supplemented with a source of choline
- Choline deficiency can lead to steatosis
- The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) published a position paper recommending that choline be routinely added to adult and pediatric parenteral nutrition formulations and stating that a commercially available parenteral product needed to be developed
  - Although the A.S.P.E.N has made this recommendation, it is not clear that it has been implemented in the treatment of patients on total parenteral nutrition

**Conclusion:** We were not able to find data regarding the extent of use of choline chloride in parenteral nutrition, if it is in fact added to parenteral nutrition

Sources of choline for parenteral nutrition are available as egg phospholipid which is primarily phosphatidylcholine or phosphatidylethanolamine (e.g., FDA-approved Intralipid 20%). The body can convert each to choline through metabolic pathways

# Clinical Effectiveness

## Atherosclerosis



- No scientific articles evaluating the use of choline chloride for the treatment of atherosclerosis and available in English were cited by the nominator. The nominator included two references for the treatment of atherosclerosis that FDA did not review because the articles were in a foreign language

# Clinical Effectiveness

## Atherosclerosis (2)



- FDA identified three studies related to choline in atherosclerosis:
  - 21 days treatment in twelve male acute myocardial infarction survivors
    - Combination of six nutrients: choline, pyridoxine, folate, cobalamin, riboflavin, and troxerutin showed reductions in cholesterol, triglycerides and LDL apo B from baseline pretreatment values (Olszewski et al. 1989)
    - Multiple ingredients in treatment prevent attributing any benefit to choline
  - 8-year cohort study of 16,165 women aged 49–70 years without prior CVD
    - To investigate the association between dietary intakes of folate, betaine and choline and the risk of cardiovascular disease (Dalmeijer et al. 2008)
    - Study failed to show any difference in cardiovascular risk between women in the highest (>329 mg/day) versus the lowest ( $\leq$  266 mg/day) quartile of dietary choline intake
  - The Atherosclerosis Risk in Communities (ARIC) cohort study in 14,420 middle-aged men and women
    - Highest (>486 mg/day) versus the lowest quartile (<298 mg/day) of total choline intake from food not significantly associated with the incidence of coronary artery disease
    - Higher choline intake was not protective for coronary heart disease

**Conclusion:** There is insufficient information to support use of choline chloride for the treatment or prevention of atherosclerosis

# Clinical Effectiveness

## Fetal Alcohol Spectrum Disorder



- Two placebo-controlled studies evaluated the developmental outcomes during the infants first year (*prenatal choline chloride exposure*) following choline chloride treatment in women who reported moderate to heavy drinking during pregnancy
- Two trials in which choline was evaluated in children for the treatment of fetal alcohol syndrome (*postnatal exposure*)

# Clinical Effectiveness - Fetal Alcohol Spectrum Disorder (Prenatal Choline Chloride Exposure)

Prospective cohort study in alcohol exposed infants during gestation (Coles et al. 2015)

- 301 pregnant women who reported moderate to heavy drinking during pregnancy compared to 313 pregnant women who reported minimal or no drinking during pregnancy were enrolled as the control population
- Randomization to three treatment groups: (1), no treatment “standard of care”; (2), supplemental multivitamins and minerals (MVM); or (3), MVM plus choline daily treatment containing 750 mg choline or 8 oral gel capsules per day
- Among participants in the choline exposed treatment arm (group 3), there was no improvement in cognitive outcome in the randomized group (mothers with moderate to heavy drinking during pregnancy) compared with the control group (mothers with minimal or no drinking during pregnancy); nor was there any difference between the group treated with only (MVM) supplement (group 2)

Conclusion: There is insufficient information to support use of choline chloride for the treatment of fetal alcohol syndrome

# Clinical Effectiveness - Fetal Alcohol Spectrum Disorder (Prenatal Choline Chloride Exposure)

Randomized, double-blind, placebo-controlled clinical trial (Jacobson et al. 2018)

- 69 pregnant women who were heavy drinkers (at least >2 drinks/day) were randomly assigned to receive a daily oral dose of either 2 g of choline or placebo from time of enrollment until delivery
- Primary outcome was eyeblink conditioning (EBC)
  - The authors concluded that infants born to choline-treated mothers “were more likely to meet criterion for conditioning on EBC than the placebo group” although it is not clear what the changes in EBC mean when interpreting neurodevelopmental outcomes in these infants
- Secondary outcome was Fagan Test of Infant Intelligence
  - At 12 months, the infants in the choline treatment arm had higher preferential looking at the novel stimulus (novelty preference scores) on Fagan Test of Infant Intelligence, indicating better visual recognition memory

Conclusion: The results are inconclusive and insufficient information to support use of choline chloride for the treatment of fetal alcohol syndrome

# Clinical Effectiveness - Fetal Alcohol Spectrum Disorder (Postnatal Choline Chloride Exposure)

**6-week, randomized, double-blinded, placebo-controlled, parallel-group clinical trial in children with fetal alcohol spectrum disorders (Nguyen et al. 2016)**

- Glycerophosphocholine liquid (Nutrasal dietary supplement) containing 625 mg choline (N = 29), or placebo (N = 26) was administered daily to children aged 5-10 years of age
- Participants in the choline group did not improve in cognitive performance in any domain compared with placebo

**9-month, double-blind, randomized, placebo-controlled pilot study (Wozniak et al. 2015)**

- Liquid choline supplement (choline bitartrate 1.25 grams containing 500 mg choline; n=31) or placebo (n=29) once daily for 9 months was administered to children aged 2.5-5 years at enrollment with fetal alcohol spectrum disorders
- The study failed on the primary endpoint of global cognitive ability

**Conclusion:** There is insufficient information to support use of choline chloride for the treatment of fetal alcohol syndrome



## Clinical Effectiveness - Conclusion

- We did not find clinical information that supported the effectiveness of choline chloride, including the nominator's proposed dosage form with route of administration using parenteral injection, for the proposed uses with respect to:
  - liver diseases (including nonalcoholic fatty liver disease), hepatic steatosis, fetal alcohol spectrum disorder, and atherosclerosis
- There is insufficient information on the effectiveness of choline chloride for supplementation in long term parenteral nutrition.

## Historical Use in Compounding

- Choline chloride has been used in pharmacy compounding since at least 1954
- Based on advertising information, choline chloride is most often used in compounded injectable products for weight loss in the US
- Choline chloride is available in the United Kingdom as part of a multiple ingredient product, Ketovite Liquid, indicated for the prevention of vitamin deficiency in certain conditions



## Recommendation

After considering the information currently available, a balancing of the four evaluation criteria weighs ***against*** choline chloride being added to the 503A Bulks List



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# Oxitriptan (5-Hydroxytryptophan or 5-HTP)

**Pharmacy Compounding Advisory Committee Meeting**

**June 9, 2021**

Madeline Wolfert, MD

Physician

Pharmacy Compounding Review Team

Office of Specialty Medicine

Office of New Drugs (OND), CDER, FDA

## Oxitriptan Evaluation Team

**Madeline Wolfert, MD**, Physician, PCRT, OSM, OND

**Lolita Lopez, MD**, Lead Physician, PCRT, OSM, OND

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

Special Thanks to:

Office of New Drugs- Division of Rare Diseases and Medical Genetics

## Nomination

- Oxitriptan, also known as 5-hydroxytryptophan or 5-HTP, is being considered for inclusion on the list of bulk drug substances for use in compounding under section 503A of the FD&C Act (503A Bulks List).
- Oxitriptan is proposed for oral use in the treatment of the rare disease, tetrahydrobiopterin (BH4) deficiency.

## Background and Regulatory Timeline

- **June 17, 2015:** Oxitriptan discussed at PCAC meeting
  - FDA evaluated oxitriptan for inclusion on the 503A Bulks List for depression and sleep disorders.
    - Did not recommend inclusion on the list due to lack of evidence of effectiveness and safety concerns, including serotonin syndrome and inadequately treated depression.
  - PCAC voted not to include on the 503A Bulks List.



# Background and Regulatory Timeline

- **December 16, 2016:** Proposed rule to not include oxitriptan on 503A Bulks List
  - FDA received comments, some of which related to oxitriptan, but none of which identified treatment of BH4 deficiency as a proposed use of compounded oxitriptan drug products
- **February 19, 2019:** Final rule published, oxitriptan not included on 503A Bulks List
  - Healthcare providers and caregivers of patients with BH4 deficiency contacted FDA expressing that oxitriptan is an essential and standard treatment for patients with BH4 deficiency.
  - FDA received a citizen petition communicating that compounded drug products containing oxitriptan are used to treat patients with BH4 deficiency
- **July 5, 2019:** FDA issued guidance explaining that it generally does not intend to take action for violations of sections 501(a)(2)(B), 502(f)(1), or 505 of the FD&C Act against compounders who use oxitriptan as a bulk drug substance to compound oral drugs for patients with BH4 deficiency, provided certain conditions are met

## Evaluation Criteria

- Physical and chemical characterization
- Clinical and nonclinical safety
- Available evidence of effectiveness or lack of effectiveness
- Historical use in compounding

## Physical and Chemical Characterization

Per the 2015 Oxitriptan Evaluation:

- It is relatively simple, well-characterized active pharmaceutical ingredient
- Likely to be stable in solid and solution formulations
- Unlikely to contain significant amounts of toxic impurities
- Oxitriptan appears acceptable for inclusion on the 503A Bulks List from a chemistry perspective

## Nonclinical Safety

Per the 2015 Oxitriptan Evaluation:

- Available nonclinical data did not identify safety concerns
  - No publicly available information on carcinogenic potential
  - Minimal available data on general toxicity, mutagenicity

## Clinical Safety

- Common adverse reactions
  - Nausea, vomiting, diarrhea, anorexia, abdominal pain, headache, and dizziness
- Potential risk of serotonin syndrome
  - Occurs with hyperstimulation of serotonin receptors in the body.
  - Symptoms include restlessness, confusion, shivering, tachycardia, hypertension, diarrhea, muscle twitches, hyperthermia, seizures, loss of consciousness, or even death.
  - Based upon mechanism of action, concomitant use of oxitriptan with antidepressant drugs could result in serotonin syndrome.

## Clinical Safety

- Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS)
  - 249 reports were identified
  - Most reports involve oxitriptan product formulated with multiple other substances, or concomitant use of other products
  - Therefore, it is not possible to determine a causal relationship between oxitriptan and the adverse event reported
  - Database has reports identifying possible serotonin syndrome

## Clinical Safety

- CFSAN Adverse Event Reporting System (CAERS) Case Report:
  - 35 y/o female taking oxitriptan and PharmaGABA-250 (gamma aminobutyric acid 250 mg) developed palpitations, elevated blood pressure, and bilateral cramping of calf muscles
  - Diagnosed with serotonin syndrome
  - Two months later, after stopping supplements, she was asymptomatic and feeling “back to normal”

## Clinical Safety

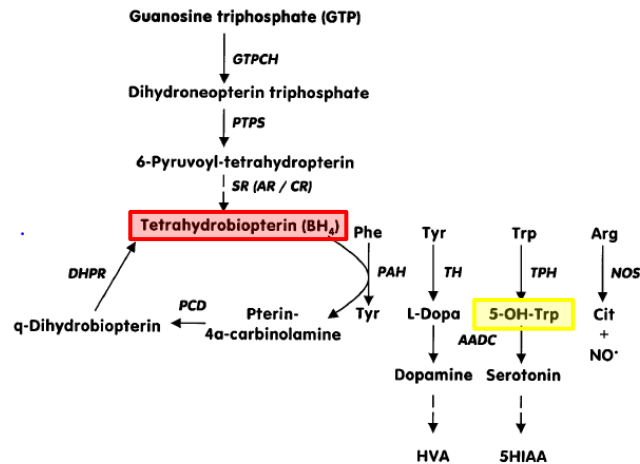
- No clinical trials to assess oxitriptan in patients with BH4 deficiency were identified
- Oxitriptan use in BH4 deficiency patients (Opladen et al. 2020)
  - Most common adverse effects were gastrointestinal symptoms (nausea, vomiting, diarrhea, etc.), irritability, motor disorders, and sweating
  - Used in combination with other medications (L-Dopa/decarboxylase inhibitor and/or sapropterin dihydrochloride/phenylalanine-reduced diet)



# Role of BH4 in the Body

- BH4 is an essential cofactor for phenylalanine hydroxylase (PAH), tyrosine hydroxylase (TH), and tryptophan hydroxylase (TPH).
- TH and TPH involved in conversion of precursors L-dopa and oxitriptan to critical neurotransmitters dopamine and serotonin, respectively.
- Disease is caused by pathogenic variants in genes encoding enzymes in BH4 biosynthesis and regeneration pathways, resulting in a depletion of available BH4.

**Fig. 1** Biosynthesis, regeneration, and functions of tetrahydrobiopterin. (*AADC* aromatic amino acid decarboxylase, *AR* aldose reductase, *CR* carbonyl reductase, *DHPR* dihydropteridine reductase, *L-dopa* 3,4-dihydroxyphenylalanine, *GTPCH* GTP cyclohydrolase, *5-HIAA* 5-hydroxyindoleacetic acid, *HVA* homovanillic acid, *5-OH-Trp* 5-hydroxytryptophan, *NOS* nitric oxide synthase, *PAH* phenylalanine-3-hydroxylase, *PCD* pterin-4a-carbinolamine dehydratase, *SR* sepiapterin reductase, *TH* tyrosine-4-hydroxylase, *TPH* tryptophan-5-hydroxylase, *PTPS* 6-pyruvoyl-tetrahydropterin synthase)



Dudsek et al. 2001

## BH4 Deficiency

- Heterogeneous group of treatable genetic neurotransmitter disorders
- Manifests with hyperphenylalaninemia and deficiency of neurotransmitter precursors, L-dopa and oxitriptan
- Diagnosis usually made based on elevated phenylalanine levels on neonatal metabolic screen

## BH4 Deficiency

- Characterized by motor dysfunction, impaired muscle tone, movement abnormalities, intellectual disability, and seizures
- Symptoms present in infancy (such as poor suck, decreased spontaneous movements)
- Rare disease
- Estimated to affect 1 in 1,000,000 individuals in the general population

## Treatment of BH4 Deficiency

- Treatment strategy described in the literature:
  - Restricted phenylalanine diet and/or BH4 replacement (sapropterin dihydrochloride)
  - Substitute depleted neurotransmitters with precursors oral oxitriptan and L-dopa/carbidopa
- Treatment should be initiated as early as possible
- Late detection and late initiation of effective treatment can lead to irreversible brain damage
- Patients with BH4 deficiency require close and lifelong follow-up

## Effectiveness of Oxitriptan in BH4 Deficiency

- Considered first-line treatment according to the International Working Group on Neurotransmitter Related Disorders (iNTD) consensus guideline and a standard therapy per National Organization for Rare Disorders (NORD)
  - Consensus Guideline for the Diagnosis and Treatment of BH4 Deficiencies lists oxitriptan as first-line treatment in combination with other treatments (Opladen et al. 2020).
  - NORD includes oxitriptan as a standard therapy to restore neurotransmitter balance.
- Recommended pediatric oral dose is 4 to 10 mg/kg/day (Bramwell 2011). Starting dose is 1 to 2 mg/kg/day, divided in 3 to 6 doses per day, with slow titration (Opladen et al. 2020).
- Dose is adjusted depending on clinical response and weight gain in pediatric patients.

## Effectiveness of Oxitriptan in BH4 Deficiency

- Case report examples in children:
  - Steady improvement in myoclonus, uncontrolled movements, hypersalivation, and head control when treated with oxitriptan and L-dopa (Bartholome 1974; Bartholome and Byrd 1975)
  - Improvement in receptive language, motor strength, increased alertness, responsiveness on carbidopa/levodopa and oxitriptan (Coughlin et al. 2012)
  - Long-term follow-up of 5 patients shows range of disease severity and variation in response (Dudesek et al. 2001)

## Historical Use in Compounding

- Has been used in compounding since at least 2011 based on published literature
- Dosing for children was first described in 1975 (Bartholome and Byrd 1975)

## Recommendation

- We have revisited whether oxitriptan should be added to the 503A Bulks List, addressing the physical and chemical characteristics, safety, effectiveness, and historical use in compounding of oxitriptan for the treatment of BH4 deficiency.
- Based on this information the Agency has considered, a balancing of the criteria weighs **in favor of** oxitriptan for oral administration being added to the 503A Bulks List.





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# **Process for Identifying Drugs for the Withdrawn or Removed List**

**Pharmacy Compounding Advisory Committee Meeting  
June 9, 2021**

**Gabrielle Cosel**  
Director (Acting)

Division of Compounding Policy and Outreach  
Office of Compounding Quality and Compliance  
Office of Compliance (OC), CDER, FDA

# Statutory Framework

- One of the conditions that must be satisfied for a drug product to qualify for the exemptions under sections 503A or 503B of the FD&C Act is that the compounder does not compound a drug product that appears on a list published by the Secretary of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (Withdrawn or Removed List), codified at § 216.24.
- A drug product that is included in the Withdrawn or Removed List is not eligible for the exemptions provided in sections 503A or 503B.



## Process for Developing the Withdrawn or Removed List

- FDA periodically reviews available information on drugs withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective with the goal of identifying possible new entries for the list.
- The information reviewed may include:
  - *Federal Register* notices announcing withdrawal of approval of a new drug application (NDA) or abbreviated new drug application (ANDA) for safety or effectiveness reasons
  - *Federal Register* notices announcing an Agency determination that a drug product that was voluntarily withdrawn from sale was withdrawn for reasons of safety or effectiveness

## Process for Developing the Withdrawn or Removed List

- FDA also reviews available information to determine whether any approvals of new drug applications would warrant modifications to existing entries on the list
- Appropriate divisions within the Office of New Drugs (OND) evaluate each identified candidate or proposed modification using the available information about the drug.
- The responsible division will prepare a review of the information that documents its recommendations as to whether to include the drug on the withdrawn or removed list, or remove a drug from the list, or modify an entry.

# Process for Updating the Withdrawn or Removed List



FDA will update the Withdrawn or Removed List through notice and rulemaking (as stated in a final rule published in October 2016).

- FDA intends to propose regulations to revise the list when we identify drugs that we tentatively determine should be listed.
- FDA also intends to propose regulations when we tentatively determine that changes to the status of drug products already on the list should result in a revision to their listing.
- Generally, FDA will finalize any additions or modifications to the list after consulting the Advisory Committee about the relevant drug, and after providing an opportunity for public comments to be submitted on a proposed rule.

## Current Drug Identified for the Withdrawn or Removed List



FDA is considering including on the list:

**Neomycin Sulfate:** All parenteral drug products containing neomycin sulfate (except for ophthalmic or otic use, or when combined with polymyxin B sulfate for irrigation of the intact bladder).



# **Review of Neomycin Sulfate for the Withdrawn or Removed List**

**Pharmacy Compounding Advisory Committee Meeting  
June 9, 2021**

**Jae Ho Hong, MD**  
Medical Officer  
Division of Anti-Infectives  
Office of Infectious Diseases  
Office of New Drugs (OND), CDER, FDA



# Outline

- Overview of Withdrawn or Removed List
- Background of neomycin sulfate
  - Description
  - Regulatory history
  - Adverse reactions with parenteral use
  - Labeled indications
- Assessment
- Recommendations

## Overview of Withdrawn or Removed List

- The Withdrawn or Removed List (21 CFR 216.24)
  - Under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA has established a list of drug products that were withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective.
- Drugs on the withdrawn or removed list cannot qualify for the exemptions under sections 503A and 503B.

## Description

- Aminoglycoside antibacterial drug, discovered in 1949
- Spectrum of activity
  - Active against susceptible strains: *P. aeruginosa*, *K. pneumoniae*, *P. vulgaris*, *E. coli*, and *E. aerogenes*
- Pharmacology
  - Poorly absorbed in the gastrointestinal tract
- Approved formulations of neomycin sulfate include oral tablets and solution, ophthalmic, otic, and dermatologic products, and a solution for bladder irrigation (in combination with polymyxin B).

## Concise Regulatory History

- Prior to 1970, approved labeling of certain products containing neomycin sulfate indicated the drug as an intramuscular (IM) injection for certain serious systemic infections and urinary tract infections (UTIs), intraperitoneal instillation for the treatment of peritonitis and in the prevention of peritonitis after intraabdominal spillage, intestinal instillation in emergency abdominal surgery, and topical use as wet dressings, packs and irrigations. (44 FR 44180)
- In 1972, FDA issued a Federal Register notice amending the labeling guidelines for neomycin sulfate sterile powder to state as follows: “Neomycin sulfate may be indicated in treatment of urinary tract infections due to susceptible strains: [*P. aeruginosa*, *K. pneumoniae*, *P. vulgaris*, *E. coli*, and *E. aerogenes*]. Because of its potential toxicity it should be reserved for hospitalized cases in which no other antimicrobial agent is effective.” The labeling guideline was also amended to include a Boxed Warning regarding nephrotoxicity, ototoxicity, and respiratory paralysis due to neuromuscular blockade. (37 FR 4224)

## Concise Regulatory History (cont.)

- In 1977, Anti-Infective Advisory Committee Meeting
  - Regarding neomycin sulfate in sterile vials for parenteral use: “...only one indication remains ... for use in urinary tract infections where other antibiotics are not effective... [The Committee] believed that there is essentially no use of the dosage form for the labeled indication... and that the risk/benefit judgement did not warrant continued marketing. They unanimously recommended that the dosage form no longer be certified. They believed that considering the potential toxicity, other drugs with less toxicity are available ...”
  - Regarding non-sterile neomycin bulk for prescription compounding: “...There is no labeling for this dosage form. It is used by hospital pharmacies and others to formulate a number of other dosage forms...The Committee concluded that a warning label should be placed on this neomycin product immediately.”

## Concise Regulatory History (cont.)

- In 1979, FDA proposed to amend the antibiotic regulations to revoke provisions for certification of neomycin sulfate in sterile vials for parenteral use based on the findings of the Anti-Infective Advisory Committee and to revoke provisions for certification of nonsterile neomycin sulfate for prescription compounding. (44 FR 44180 and 44 FR 44178)
- In 1988, FDA revoked the provisions for certification of neomycin sulfate in sterile vials for parenteral use and, as a result, neomycin sulfate packaged in sterile vials for dispensing could no longer be certified or released. (53 FR 12658)
- In 1988, FDA amended the provisions for certification of non-sterile neomycin sulfate for prescription compounding by changing the product name to “neomycin sulfate for compounding oral products” and to require labeling to provide information concerning appropriate uses and to warn about the risks associated with inappropriate use. (53 FR 12644)

## Concise Regulatory History (cont.)

- In 1988, FDA proposed to withdraw and subsequently withdrew approval of four applications for neomycin sulfate in sterile vials for injection. The application holders waived their opportunity for a hearing. (53 FR 12664 and 53 FR 49232)
- In 1988, FDA proposed to withdraw six applications for nonsterile neomycin sulfate products for prescription compounding and subsequently withdrew five of these applications whose holders waived their opportunity for a hearing and did not submit supplemental applications. (53 FR 12662 and 53 FR 49231)
- In 2019, FDA withdrew approval of the last application for neomycin sulfate for prescription compounding. The holder of this application had waived its opportunity for a hearing. (84 FR 1746)

# Adverse Reactions of Neomycin Sulfate with Parenteral Use

- **Nephrotoxicity**
- **Ototoxicity (manifested as irreversible sensorineural hearing loss)**
- **Neuromuscular blockade and respiratory paralysis**



# Currently Approved Indications for Oral/Irrigational Neomycin Sulfate Products

- **Neomycin Oral Tablet:**
  - Adjunctive therapy in hepatic coma (portal-systemic encephalopathy)
  - Adjunctive therapy as part of a regimen for the suppression of the normal bacterial flora of the bowel (e.g., preoperative preparation of the bowel)
- **Neomycin Oral Solution:**
  - Adjunctive therapy in hepatic coma (portal-systemic encephalopathy)
- **NEOSPORIN G.U. Irrigant (neomycin sulfate in combination with polymyxin sulfate solution for irrigation):**
  - Short-term use (up to 10 days) as a continuous irrigant or rinse in the urinary bladder of abacteriuric patients to help prevent bacteriuria and Gram-negative rod septicemia associated with the use of indwelling catheters.

WARNINGS note: "...should not be given where there is a possibility of systemic absorption...should not be used for irrigation other than for the urinary bladder."

## Assessment of Neomycin Sulfate

- The overall assessment of the approved formulations of neomycin sulfate, including formulations for oral administration, ophthalmic, otic or dermatologic use, and in combination with polymyxin B sulfate for irrigation of the intact bladder, remains favorable.
  - Systemic exposure to neomycin sulfate associated with the irrigation of the intact bladder has been found to be minimal.\*
- All other parenteral neomycin sulfate formulations may result in significant systemic exposure to neomycin and be associated with serious adverse reactions (ototoxicity, nephrotoxicity, neuromuscular blockade leading to respiratory paralysis).

\*de Jong TP, Donckerwolcke RA, Boemers TM. Neomycin toxicity in bladder irrigation. J Urol. 1993 Oct;150(4):1199.



## Recommendations

FDA recommends that the following entry for neomycin sulfate be added to the Withdrawn or Removed List:

*Neomycin Sulfate: All parenteral drug products containing neomycin sulfate (except when used for ophthalmic or otic use or in combination with polymyxin B sulfate for irrigation of the intact bladder).*



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