Background:
The IHS National Pharmacy & Therapeutics Committee (NPTC) recently reviewed various nutritional supplements used for women’s health including folic acid, calcium and vitamin D. The review included guideline recommendations and published literature on the use of folic acid in preventing neural tube defects, the role of calcium and vitamin D in preventing osteoporotic fractures and the emerging role of calcium in preventing pre-eclampsia. Vitamin D and calcium are listed on the National Core Formulary (NCF). The NPTC added folic acid (any product containing ≥400 mcg/daily dose) to the NCF. Calcium (any formulation) and vitamin D (any product) are currently on the NCF.

Discussion:
Folate is a water-soluble B vitamin (vitamin B9) naturally present in beans, beef liver, whole grains, vegetables, and fruits. Folate functions as a coenzyme in synthesis of DNA and RNA and metabolism of amino acids and a lack of folic acid in the diet of pregnant women has been associated with neural tube defects in their offspring. In 1998, the FDA mandated fortification of all enriched grain products resulting in a 27% decrease in neural tube defects. It is estimated that folic acid fortification prevents 1300 births with neural tube defects per year (MMWR, 2015). In addition, systematic reviews have shown that folic acid supplementation in mothers reduce neural tube defects in offspring without causing adverse effects in mothers or babies (De-Regil, 2010). Therefore, the American College of Obstetricians and Gynecologists (ACOG) recommends that all women of child bearing age consume 400 mcg/d of folic acid and those with high risk of neural tube defects or a previous infant with a neural tube defect to consume 4mg/d (ACOG, 2013).

Calcium is the most abundant mineral in the body and is required for vascular and muscle function, nerve transmission, intracellular signaling, and hormonal secretion. However, 99% all of the body’s calcium supply is stored in bones and teeth, supporting their structure and function. The recommended daily allowance for calcium is 700-1,300 mg/day, depending on age (NIH 2015) which is also endorsed by the ACOG Osteoporosis guidelines. The Institute of Medicine (IOM) recommends 1000-1200 mg of calcium daily for females depending upon age and 1300 mg of daily calcium for pregnant or lactating women younger than 18 years of age.

Studies regarding calcium supplementation with or without the addition of vitamin D in the primary prevention of osteoporotic fractures have had mixed results. In a meta-analysis, calcium or calcium with vitamin D was associated with reduced bone loss and a 24% risk reduction of fractures in trials with >80% compliance (Tang, 2012). In a study involving postmenopausal women given 1000mg calcium with vitamin D3 daily versus placebo, supplementation resulted in a small but significant improvement in hip bone density. However, there was no significant reduction in hip fractures and authors noted an increased risk of nephrolithiasis (Jackson, 2006). A more recent systematic review evaluated studies published between 2005 and 2011 and concluded that there were no differences demonstrated between calcium alone and placebo in reducing fracture risk, or between calcium or vitamin D alone in reducing vertebral, hip, or other non-vertebral fracture risk. Calcium with vitamin D (>800 units) was shown to reduce fracture risk only in institutionalized (long-term healthcare facility) patients (AHRQ, 2012).

Calcium has also been studied to treat hypertension and preeclampsia in pregnant mothers. In a recent Cochrane review, calcium supplementation demonstrated a reduction in the risk of hypertension and preeclampsia compared with placebo (Hofmeyr, 2014). However, current ACOG recommendations regarding calcium supplementation in the treatment or prevention of hypertension in pregnancy continues to confine
calcium supplementation to those patients known to have a low calcium diet, and ACOG does not presently consider the United States (U.S.) diet to be at risk (ACOG 2013).

Vitamin D is a fat soluble vitamin produced naturally in the skin as vitamin D3. Alternatively, vitamin D can be supplemented with vitamin D3 (cholecalciferol) or vitamin D2 (ergocalciferol). Vitamin D deficiency was estimated to be as high as 41.6% in US adults in one study (Kimberly, 2011). For adults aged 18-70 years, the IOM recommends 600 units daily and 800 units daily for those over 70 years. Supplemental doses of vitamin D recommended are based on age for patients at risk of vitamin D deficiency:

- 0-1 years: ≥400 units daily; children 1-17 years: 600 units daily; adults 18-50 years: 600 units daily; adults >50 years: 600-800 units daily; and pregnant or lactating women: 600 units daily (NIH 2015)

Though one meta-analysis has shown that vitamin D supplementation reduces falls by 22% in the elderly, (Bischoff-Ferrari, 2004), a recent U.S. Preventive Services Task Force (USPSTF) meta-analysis demonstrated no significant reduction in fractures in studies with 1000mg calcium plus 400 IU Vitamin D3. Furthermore, trials with vitamin D alone showed no statistical differences (Moyer, 2013). The USPSTF concluded that there is currently insufficient evidence to assess the balance of benefits and harms of combined calcium and vitamin D supplementation for: (1) primary prevention of fractures in elderly men or premenopausal women and; (2) for supplementation greater than 1000 mg calcium and 400 IU vitamin D3 for the primary prevention of osteoporotic fractures.

There is also contradictory evidence on which vitamin D formulation is most effective at increasing serum vitamin D levels. Though both forms are regarded as equivalent based on their ability to cure rickets, some data suggests cholecalciferol (D3) raises serum calcidiol levels more effectively than ergocalciferol (D2) and, at high doses, ergocalciferol appears to be less potent. At present, the most effective dose, formulation and dosing interval has not been adequately studied (Barton, 2014).

Findings:
Folate supplementation for prevention of neural tube defects is beneficial and recommended in all women of childbearing age, thus **folic acid (any product with >400 mcg/daily dose) was added** to the NCF. Studies have not demonstrated a definite benefit of calcium and vitamin D supplementation in reducing fracture risk in postmenopausal women or the elderly with osteoporosis. However, recommendations for calcium and vitamin D are present in multiple guidelines for prevention of development of osteoporosis. Calcium (any formulation) and vitamin D (any product) are currently on the NCF.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the **NPTC website**.

References:
7. CDC. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR Rep 2015;64 (No. RR-64).