Model-Based Meta-Analysis to Develop a Vitamin D Parent-Metabolite Population-Pharmacokinetic Model

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**Objectives:** Association of Vitamin D (D3 & D2) and its 25OHD metabolite (25OHD3 & 25OHD2) exposure with various diseases is an active research area [1]. Clinical studies variations, including dosing regimen, assays, demographics, and control of endogenous D3 production, lead to uncertain and conflicting exposure-related associations. Dose-equivalency of D3 and D2 is also under debate. Population PK (PPK) models were developed to predict D and 25OHD to provide comparisons of D3 and D2 exposures and an added understanding of variability related to dose, baseline and assay type.

**Methods:** Public-source PK data pertaining to D and 25OHD in healthy or osteoporotic populations, including 74 studies representing 5684 individuals (40 individual-level and 140 group-level units), were selected using specified search criteria in PUBMED. Data included IV, oral, single and multiple dose: dose ranges for D3 (400-100000 IU/d), D2 (400-100000 IU/d) and 25OHD3 (15-1000 ug/d). Nonlinear mixed effects models were developed simultaneously for D and 25OHD PK (NONMEM v7.2). Model development explored 1- and 2-compartment models with linear (CL) or nonlinear clearance (CLNL). Unit-level random effects and residual errors were weighted by arm sample size.

**Results:** D2 and D3 parent and metabolite were each described by 2-compartment models with numerous shared estimates (Figure 1). D3 CLNL resulted in inverse 25OHD3 relationships with dose and baseline; D2 did not exhibit nonlinearity. Quadrupling D3 dose (400 to 2000 IU/d, 25OHD3 baseline=40 nmol/L) resulted in only a 1.3 fold 25OHD3 increase. Precision and bias differences for 25OHD3 competitive protein binding assay and chemiluminescence suggested that assay be considered when comparing these with RIA or HPLC-MS.

**Conclusions:** D3 and 25OHD3 PK modeling suggested that CLNL was important when considering these exposure comparisons across studies and dosing regimens. Notable D2/D3 differences included CLNL for parent D3 and higher (nearly doubled) estimated D2 metabolite CL.

**References:**

**Figure 1.** a) Compartmental model for D (D2 & D3) and 25OHD (25OHD2 & 25OHD3) with parameter values* (red = D3, purple = D2, black = shared) b) Diagnostic plot for 25OHD2 and c) 25OHD3

*ENDOG = endogenous D3 production; BL = baseline concentration