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Title: Systemic Concentrations Can Limit the Oral Absorption of Poorly Soluble Drugs: An Investigation of Non-Sink Permeation Using Physiologically Based Pharmacokinetic Modeling

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Abstract:

Oral bioavailability is often described limited by factors such as the permeability, solubility, dissolution rate, chemical stability, and metabolism of the drug. Among those factors; solubility and dissolution rate of a poorly water-soluble drug are considered as the most critical factors. In the past decade, there has been an increasing challenge for the pharmaceutical industry in achieving reasonable bioavailability after oral delivery of poorly water-soluble drug candidates. Despite the efforts, many cases proved unsuccessful where in vitro improvement does not directly translate into in vivo. One common theme was that all of the above efforts were based on the assumption of oral absorption of the drug is limited by the solubility in GI. Furthermore, the sink condition is always used for exposure modeling where non-sink condition was not considered especially for chronic doses. In our study, a non-sink condition was established in vivo via infusion with nanosuspension of crystalline Deuterated model drug DCU targeted to a certain percent of saturated plasma solubility and then follow by oral dosed of regular DCU. Pharmacokinetic modeling was performed to estimate the impact of absorption with pre-circulated drug. It was found that oral absorption of DCU decreased where pre-circulated drug exist.

Speaker Bio:

Tom Chiang Ph.D. has been working in the Pharmaceutical industry for over 25 years. His research interests are focused in the area of preclinical drug delivery, PK, PK/PD, and Biopharmaceutics modeling to support both clinical and pre-clinical studies. He has published more than 35 articles in peer reviewed journal and he is the editors for 5 different journals. Currently, he is a Senior Scientist at Genentech. His main function is to support small molecule drug discovery and development.