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Diagnose Absorption Risks Early to Improve Preclinical and Clinical Outcomes with PBPK Modeling

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Poor oral absorption properties in drug candidates can delay critical preclinical and clinical studies, leading to inflated timelines and costs for drug manufacturers. However, utilizing physiologically based pharmacokinetic (PBPK) models to better predict study outcomes can help sponsors understand obstacles to absorption. As a result, they can formulate strategies for improving absorption and reducing associated risks prior to conducting in vivo studies.

In a recent webinar hosted by Lonza, Deanna Mudie, Ph.D., Senior Principal Engineer at Lonza Small Molecules, and John DiBella, President of Simulations Plus, both discuss the broad potential impact of utilizing PBPK for risk assessment, sharing multiple PBPK case studies. Below, Deanna and John share their insights with webinar attendees on the impact of solid form changes and other solutions that can emerge from PBPK findings.

Q: How do you change from crystalline to amorphous solubility in GastroPlus®?

John DiBella: Starting with a couple of the more recent versions of GastroPlus®, we have extended the options to be able to enter multiple polymorph solubilities into the software. You have the flexibility to be able to either start off and define the amorphous form solubility or whatever the form of the drug is in formulation

and use that for the duration of the simulation. If there is any precipitation that may be taking place, [you can say] I want it to precipitate into a different polymorph form and enter that solubility as well. The program would then, for the precipitate material, use different solubilities for calculating the redissolving of that drug.

You also have a lot of flexibility in terms of defining, in the formulation itself, multiple solubilities. If you have different ratios of an amorphous and crystalline form in the product, you would be able to set up multiple solubility inputs and use that to drive the predictions for dissolution and precipitation. That is all available on the main compound window of GastroPlus® next to where you enter the reference solubility. There is a button that says, "More Solubility" where you have the flexibility to work with these different forms.

Q: Was the effect of changing gastric pH on absorption of posaconazole predicted and validated? And if so, what were your findings?

Deanna Mudie: When we looked at the impact of gastric pH on posaconazole with a parameter sensitivity analysis, we saw quite a big dependence with the crystalline Noxafil oral suspension (OS)®. We did confirm that with in vitro dissolution testing as well as some solubility assessments. What we found also was that the amorphous form was way less sensitive due to the high increase in solubility at the moderate pH level. In terms of our in vivo dog study, we only conducted that with pentagastrin treated dogs with a very low gastric pH. However, there was another study in the literature where they had dogs that did not have a pretreated stomach, so chances are that their gastric pH was ranging anywhere from about one to eight. In that case, we saw a much higher amorphous enhancement than we did with the crystalline form, as expected, due to the large decrease in performance when Noxafil OS® is administered at higher gastric pH.

Q: How do you choose which in vitro test you're going to use for a particular formulation?

Mudie: It really comes down to what we think the rate determining step to absorption is or what the problem statement is early on. We can determine that based on things like the fraction absorbed classification system that takes into account the dose, dissolution rate, and solubility in the species of interest. We'll tailor our dissolution test to study dissolution rate, precipitation rate, or the impact of dissolved species on absorption. We make sure that we're really capturing that critical step so that we can enter that information into the PBPK model.

DiBella: There has been some really good literature that's been published where you could also think about this in the reverse way; as you do one of the first animal tests, perform a deconvolution to find out what the in vivo release of the original formulation was, and use that as a target to then identify which in vitro method does the best job of predicting what the in vivo exposure for that formulation is. If you've done a couple of early PK studies and have some of that data available, make use of it. Reverse engineer [to determine] what the in vivo release was and use that as a guide to help design the in vitro experiments so that you have more confidence in the next round of simulations to be performed.

Q: What were the agents for dogs to change the gastric pH?

Mudie: Dogs were pretreated with intramuscular pentagastrin in Phases 1 and 3 to increase gastric acid secretion and lower stomach pH (representing fasted human gastric pH), and dogs were pretreated with oral famotidine in Phases 2 and 4 to decrease gastric acid creation and raise stomach pH (representing the gastric pH of fasted humans taking ARAs).

Q: Can you think of an example of using ADMET/G%2B to make choices regarding an animal study as opposed to confirming expected output?

Mudie: Yes, for the acalabrutinib case study reviewed in this webinar, we used ADMET Predictor combined with GastroPlus a priori to select the administered dose and type of gastric pretreatment expected to meet our objectives of 1) mitigating the pH effect using an amorphous solid dispersion (ASD) tablet, 2) matching plasma exposure of fasted CALQUENCE® using the ASD tablet, and 3) showing a pH effect using CALQUENCE.

To watch the full webinar and Q&A session hosted by Lonza Small Molecules, please click here.