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https://www.certara.com/case-study/ddi-regulatory-poster-child-using-the-simcyp-simulator-ibrutinib-imbruvica/

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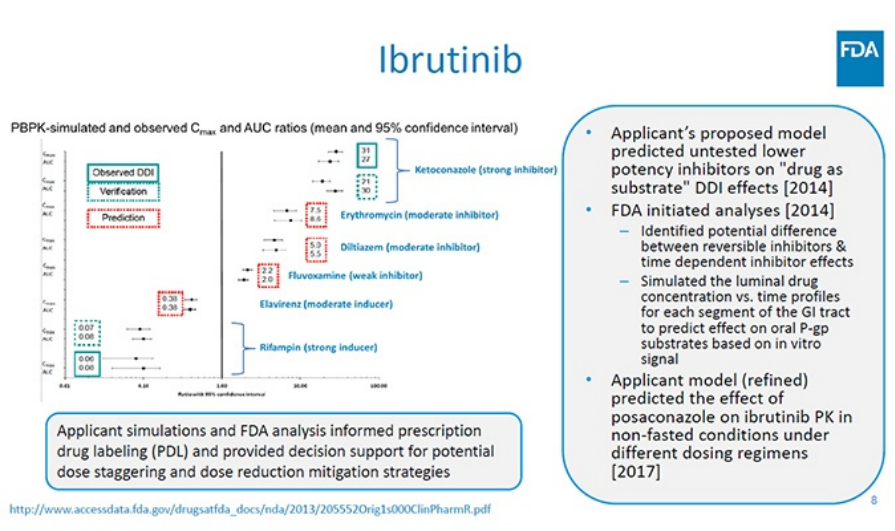
CASE STUDY

DDI REGULATORY POSTER CHILD USING THE SIMCYP SIMULATOR: IBRUTINIB (IMBRUVICA®)

Pharmacylics and J&J sought to bring ibrutinib, its new tyrosine kinase inhibitor therapy targeting rare B-cell malignancies to market. The company leveraged FDA's accelerated approval program; it was one of the first to be awarded breakthrough status by the agency. Ibrutinib is susceptible to interactions with a strong inhibitor and inducer of CYP3A4 enzymes, thus posing potential drug-drug interactions (DDI). Additionally, a dose optimization approach was needed to adjust the regimen for cancer populations.

Models built in the Simcyp Simulator using in vitro data were validated using clinical data on the observed effects of both a strong CYP3A4 inhibitor and a strong inducer on ibrutinib exposure. Simulations then predicted the effects of a moderate CYP3A4 inducer and other CYP3A4 inhibitors (strong, moderate, and weak) on ibrutinib exposure, as well as investigating the impact of dose staggering and dose adjustment. The final drug label included 24 individual claims for untested DDI scenarios (without the need for clinical trials) and provided a dose optimization strategy aligned to individuals with different metabolic profiles.



> "The simulations of PBPK model provided a dose optimization strategy for combined use of ibrutinib with specific CYP3A inhibitors or inducers."
>
> **from the FDA label report, June 28, 2013**

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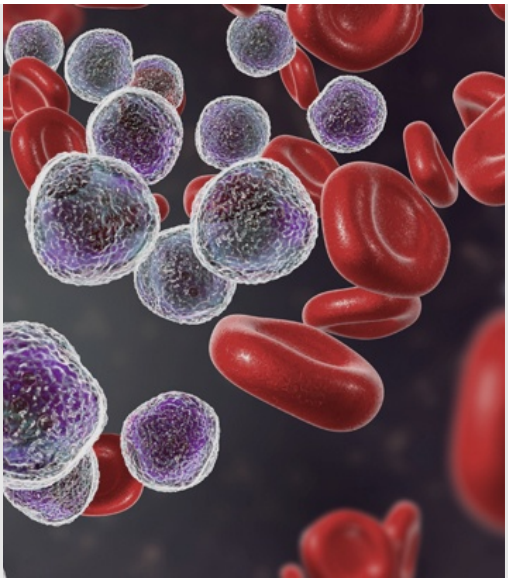
CASE STUDY

While in 2013 the use of PBPK to predict DDIs, inform drug labels and eliminate the need for in vivo trials was quite novel, it is now an 'expected' or 'encouraged' approach. As outlined in the new guidance and shown in this case study, the extrapolation from itraconazole and rifampin studies provide dosing guidance on intermediate scenarios using PBPK. In fact, the regulators cite the use of PBPK for Ibrutinib as a 'best practice.'

Initially approved by the US FDA in 2013 for mantle cell lymphoma as a breakthrough therapy, ibrutinib, marketed as Imbrivica®, was recently approved by the US FDA for its 11th indication. The drug has treated almost 200,000 oncology patients in 100 countries.



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