One of the key tasks of the healthcare system is to ensure access to therapies that are primarily effective and safe. However, the financial aspect of their costs remains equally important, as it can be a significant factor that limits accessibility. Lowering drug prices can be achieved by increasing competitiveness (among others), which is often reached as a result of the availability of a larger number of so-called *generic drugs*. The registration of an original drug requires several, sometimes even dozens years of work, and the cost of bringing a single drug to the market is estimated to be billions of PLN. To ensure the profitability of the process, new molecules are protected by patents, in the case of drugs typically for 25 years. After this time, competing companies can introduce generic drugs to the market, commonly known as *substitutes*. They contain the same active pharmaceutical ingredient(s) (APIs) and release it in the same way, making them bioequivalent to the original product and therefore having the same safety and efficacy profile. Due to the fact that a generic drug is based on an already tested molecule, its manufacturers can reduce the number of studies and, as a result, reduce the time and money required to introduce it to the market. Lower investments in drug development ultimately allow for a lower market price.

To support the entry of generic drugs into the market, science focuses on the continuous development of technologies that enable efficient bioequivalence testing. Computer-based methods, which replace some of the laboratory experiments, are being increasingly utilized. One of these techniques is the physiologically-based pharmacokinetic (PBPK) mathematical modeling. Such models, by combining detailed drug, human body and study data, allow for calculation-based predictions of plasma drug concentration changes after a drug administration to a patient.

In recent years, scientific research has focused on the aspect of predicting drug penetration through the skin using various models. As a result of these efforts, the MPML MechDermA model was published, which allows for predicting the penetration of a drug applied to human skin, both in living organism and in vitro permeation testing (IVPT) conditions, where the drug penetration is studied on excised skin fragments. In 2021 Tsakalozou et al. described the application of such a model to support the market entry process of a generic diclofenac gel in the United States.

Porcine skin is often used interchangeably with human skin in IVPT studies due to anatomical similarity. To expand the applicability of the MPML MechDermA model, we initiated a project aiming in its adaptation to the properties of porcine skin. The model has already been developed and its utilization is currently being investigated. Caffeine was chosen as the first test substance and the model was built to predict its permeation from aqueous solutions in IVPT conditions.

The aim of our project is to develop a PBPK model that will allow prediction influence of the quantitative and qualitative differences in caffeine solution compositions on its permeation through porcine skin. The work will combine both laboratory research and experiments using computational methods.

The planned laboratory work will involve preparation of various caffeine solutions, measurement of their physicochemical properties such as viscosity and pH, and then investigation of the permeability of caffeine from these solutions through porcine ear skin in IVPT conditions. The obtained results, together with the literature data, will enable construction and verification of the PBPK model. The first stage of this research will allow to test the predictive performance of the existing model for aqueous solutions. Then, the physicochemical properties data will be used to develop a model that will predict differences in caffeine permeability depending on solution composition. In the subsequent stage, experiments on porcine skin and computer simulations will be conducted simultaneously under the same experimental conditions. This will allow for verifying whether the computer calculations provide results corroborate the laboratory data.

The validated model will be used for further investigation of factors influencing caffeine permeation through the skin. Such models are important not only from the perspective of developing new medicinal products, but also for the cosmetic industry and the study of the safety of various substances. In future, this approach may significantly reduce the number of experiments involving human and animal skin. Moreover, it may enable more effective prediction of the impact of substances on humans based on studies conducted on animal skin.