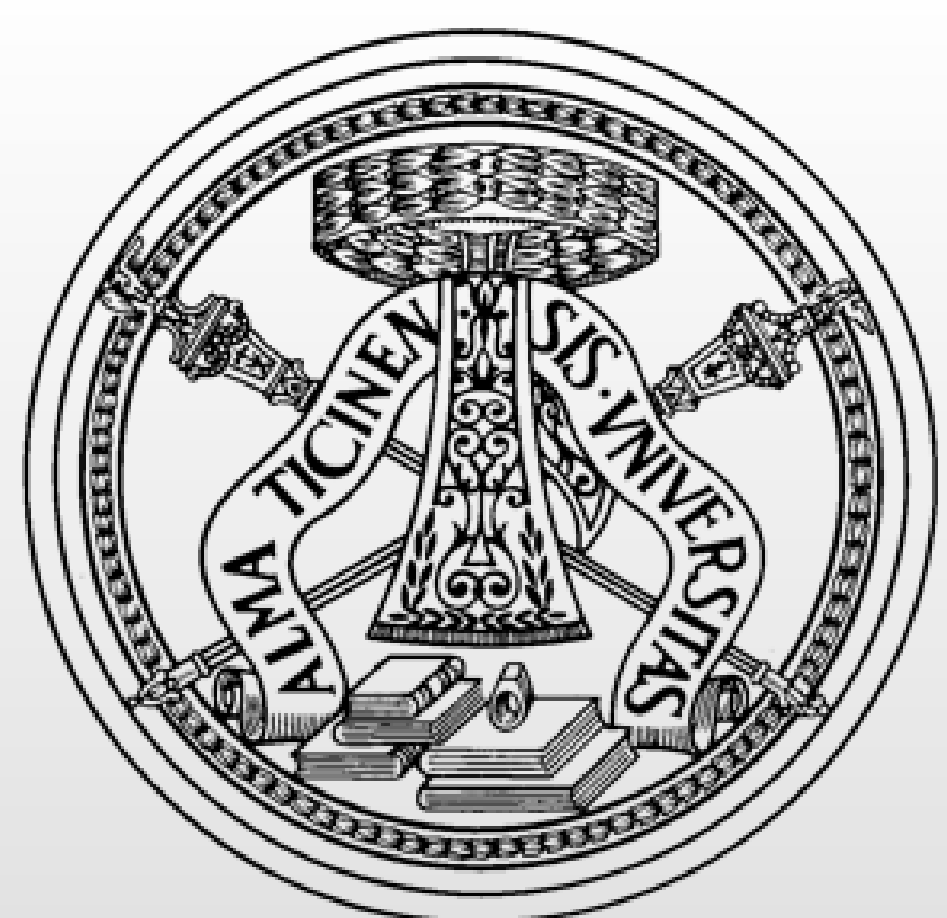




Evaluating the inclusion of the particle size distribution in the lung dissolution model of a WB-PBPK model to describe the pharmacokinetics of inhaled polydisperse drugs

Silvia Grandoni¹, Nicola Cesari², Giandomenico Brogin²,
Paola Puccini², Paolo Magni¹

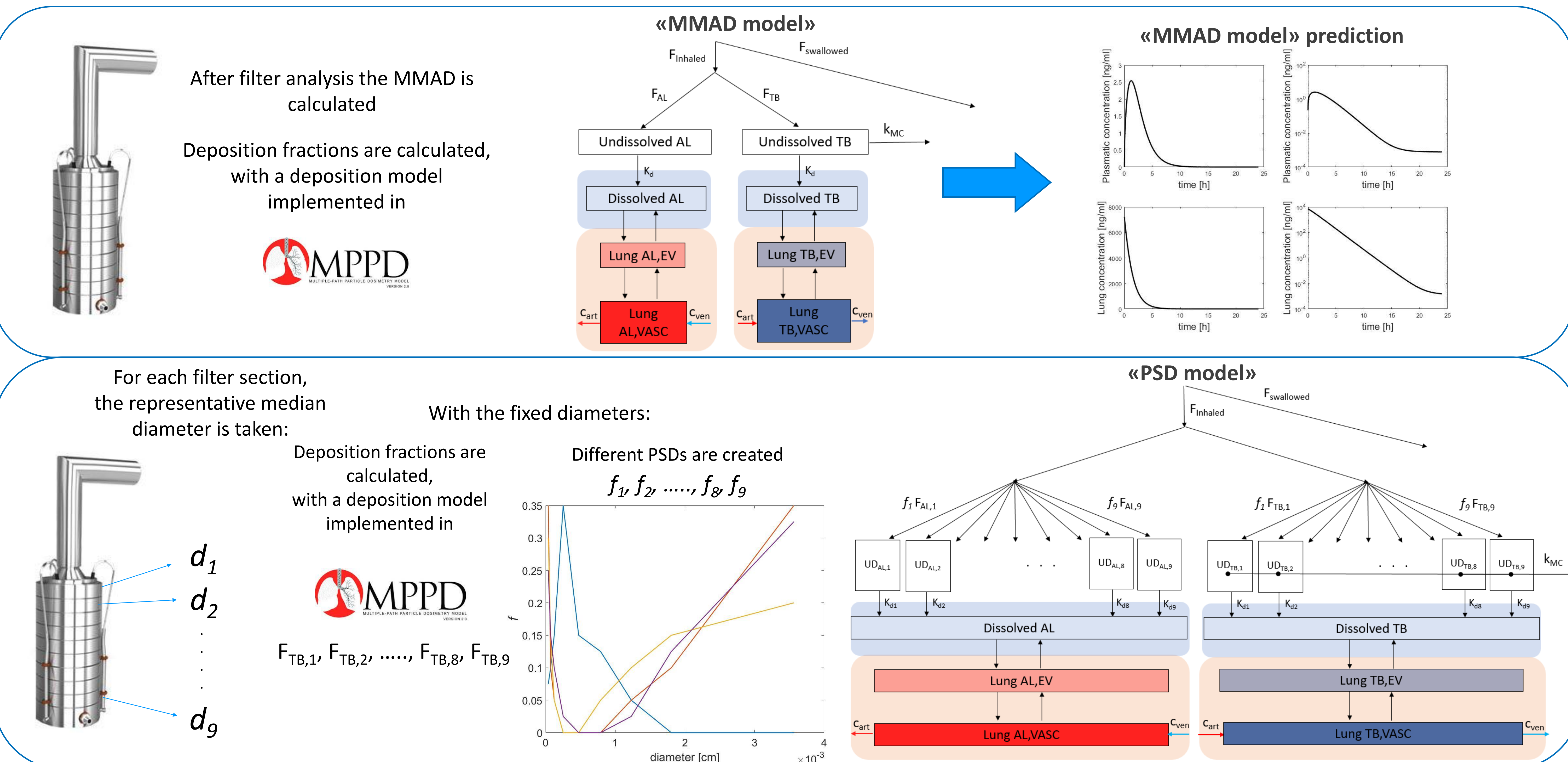
Università degli Studi di Pavia

¹BMS Lab, Department of Electrical, Computer and Biomedical Engineering, University of Pavia (Italy),

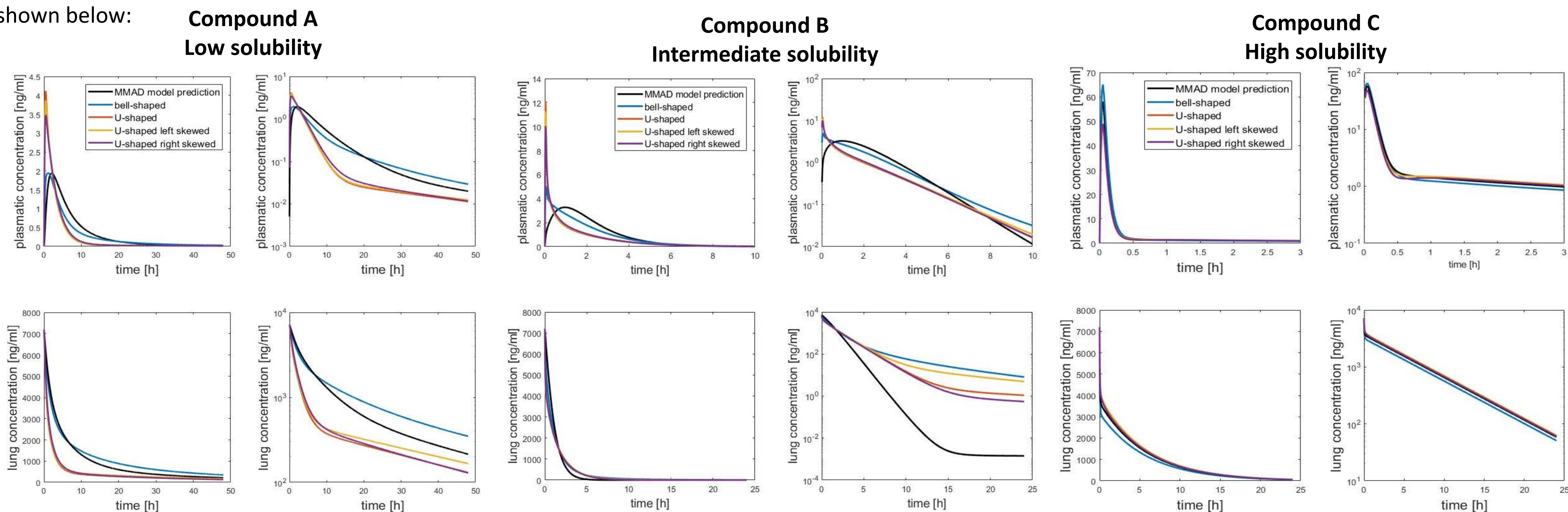
²Chiesi Farmaceutici S.p.A, Parma (Italy)

OBJECTIVES: evaluating the impact of the particle size distribution (PSD) of a polydisperse powder of inhaled drugs, compared to a monodisperse powder with particle size equal to the Mass Median Aerodynamic Diameter (MMAD) on the lung and plasmatic concentration-time profiles derived with a WB-PBPK model.

METHODS: administration of inhaled drugs was added to a previous developed and validated WB-PBPK model [1]. In particular, the lung was modelled considering its two main anatomical regions, the central (C) and the peripheral (P) one; each of these was further divided in three sub-regions to take into account the main physiological process occurring when a drug is inhaled, i.e. deposition, clearance, dissolution and absorption [2]. The dissolution has been modelled with the Nernst-Brunner equation [3], the mucociliary clearance has been included as acting in the C region only, as a first order process, and the absorption has been described as a first order process with an absorption rate constant depending on the surface area of the region and on the permeability of the drug. The model was implemented in MATLAB™ in two versions which differ in the dissolution modelling only, in particular, in the “PSD model” to consider the PSD in the dissolution, the undissolved state compartments were divided in several sub-compartments each of them containing an amount of monodisperse drug with a different diameter, while in the “MMAD model” the particles are considered as monodispersed, with a diameter equal to the MMAD. A series of intratracheal experiments were simulated in rats to compare the two models, different PSD scenarios were reproduced, with the same MMAD.



RESULTS: simulating with the bell-shaped distribution the differences are negligible, simulating with the U-shaped PSDs, differences from the plasmatic and lung concentration-time profiles obtained using the MMAD only occur, in particular, the presence of earlier and higher plasma peaks is observed. Examples of the comparison between the plasmatic concentration-time profile obtained using the MMAD only and the particle size distributions in the dissolution model are shown below:



CONCLUSIONS: with the here proposed WB-PBPK model, differences between the PK profiles obtained considering the particles as monodispersed and represented by their MMAD and those obtained including the PSD in the model, occur only in some cases of U-shaped distributions, especially for the scenarios of lower solubility. Considering that actually the PSD of the powders is typically bell-shaped and centred around the MMAD, the use of the MMAD only in the dissolution model seems to be, in this context, sufficient to describe the powder particle size in the lung dissolution process.

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