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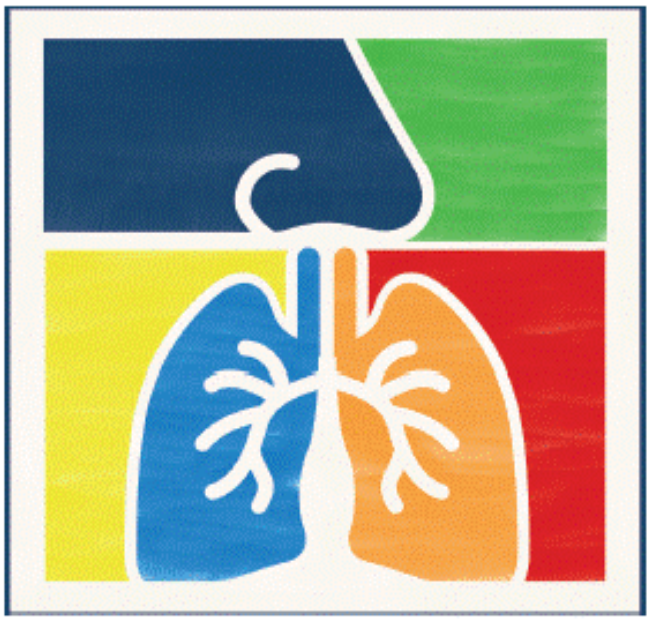
Respiratory Drug Delivery



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An *In Silico* Modeling Framework to Predict Particle Dynamics in Dry Powder Inhalers

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SUMMARY

The administration of medicines via inhalation is one of the most common treatments for patients with chronic obstructive pulmonary disease (COPD). Capsule-based dry powder inhalers (DPIs) are widely used to deliver active pharmaceutical ingredients (APIs) attached to micron-sized carrier particles into the human respiratory system. To evaluate the drug delivery effectiveness of DPIs, a model has been developed based on computational fluid dynamics (CFD) and the discrete element method (DEM) to simulate the agglomeration/deagglomeration, transport, and deposition of carriers and APIs in the DPI flow channel and human respiratory system. In this study, the CFD-DEM model has been applied to evaluate the comparability of a potential generic DPI (Cipla) and Spiriva™ Handihaler™ (SH) (Boehringer Ingelheim, Germany) based on their (1) device delivery efficiencies, (2) emitted aerodynamic particle size distribution (APSDs), and (3) regional lung depositions. The *in silico* CFD-DEM model potentially provides a demonstration of how to fully utilize *in vitro* and clinical data in CFD and DEM simulations to obtain new insights into the transport dynamics of APIs in DPIs and lungs, thereby representing a possible approach to reduce the cost of generic product development.

INTRODUCTION

Documentation of comparability between generic inhaler design and performance and that of the reference listed drug (RLD) product is essential for regulatory approval of the generic product. The capability to accurately predict particle transport, interactions, and deposition in the human respiratory tract using high-fidelity numerical methods are valuable data for regulators to consider during the market authorization of orally inhaled drug products (OIDPs), such as DPIs. Predictive models must accurately predict particle-particle agglomeration/deagglomeration, as well as particle-(airway) wall interactions. To explicitly model the particle-particle and particle-wall interactions, this study developed a CFD and DEM to examine drug delivery efficiency, determine emitted APSDs, and quantify the resultant lung depositions of both lactose carriers and API particles. Numerical parametric studies were also performed with multiple steady, simulated inhalation airflow rates through the DPI, carrier shapes, and DPI designs. Spiriva Handihaler and a potential generic DPI (Cipla) were evaluated in this study. Simulations have been done to unveil the performance of carriers and APIs in the two DPIs in a low-risk, time-saving virtual environment, which can potentially develop innovations faster at a lower cost. Our long-term goal is to use the CFD-DEM model in the early stages of the device development process in advance of, and to complement, *in vitro* and *in vivo* studies.

METHODOLOGY

The objective of this study is to develop and test a computational model to predict relationships between DPI design, carrier shape, simulated, steady inhalation airflow rate through the DPI, and the drug delivery efficiency to specific lung regions, i.e., after the 13th airway generation (G13). SH (containing tiotropium bromide) as the RLD and a generic DPI candidate were selected for the comparability assessment case study (see Figures 1(A) and (B)), as both products are single-dose, capsule-based devices, which can cover a broad range of inhalation flow rates [1]. The evaluation of the comparability between the generic DPI and SH has been numerically evaluated by comparing the DPI delivery efficiencies, emitted APSDs, and the resultant lung deposition patterns. An experimentally calibrated and validated CFD-DEM method [2] was employed to predict agglomeration and deagglomeration of carriers and APIs. Utilizing the time-saving and cost-effective CFD-DEM model, simulations were performed at steady inhalation flow rates of 30, 39, 60, and 90 L/min [3]. Simulations were performed on spherical particles and sphero-cylindrical lactose carriers with an aspect ratio (AR) equal to 5 and 10.

The resultant depositions of API and carriers in a 3D human respiratory system (see Figure 2) were simulated using the validated Euler-Lagrange-based CFD model [4–13]. We considered API deposition after the G13 to be an important feature of DPI efficiency, because particles that escape from G13 outlets are considered deposited in the small airways with diameters less than 2 mm [14, 15]. Such airways are the target of many OIDPs. Therefore, this study provides an *in silico* prediction of fundamental carrier-API interactions in DPIs, and the effect of carrier shape and DPI flow channel designs on the drug delivery efficiency from DPIs and deposition patterns in the human respiratory system.

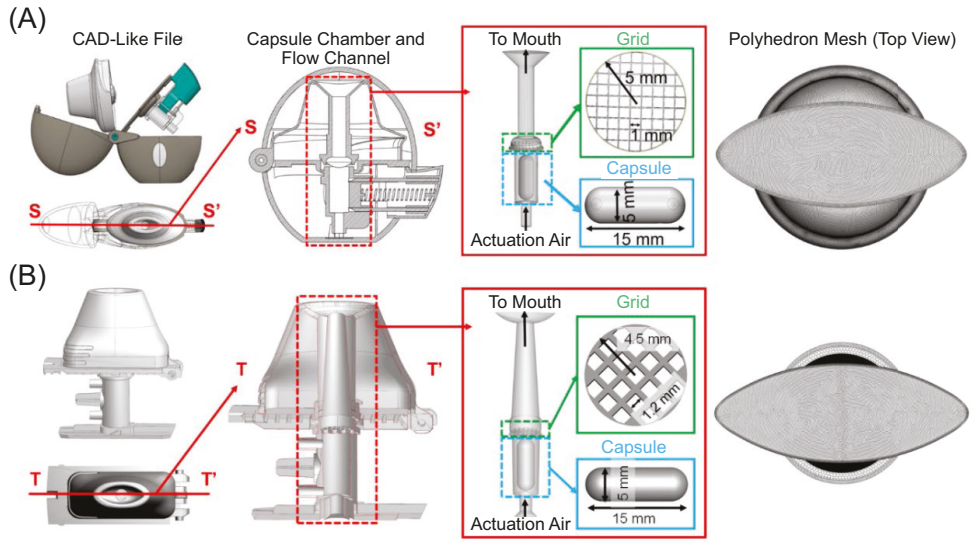

Figure 1. Computational DPI geometries and the hybrid polyhedral meshes, including the flow channels, grids, and capsules for DPI simulations modeling actuation airflow as steady-state inhalation at multiple flow rates: (A) SH, and (B) the generic DPI.

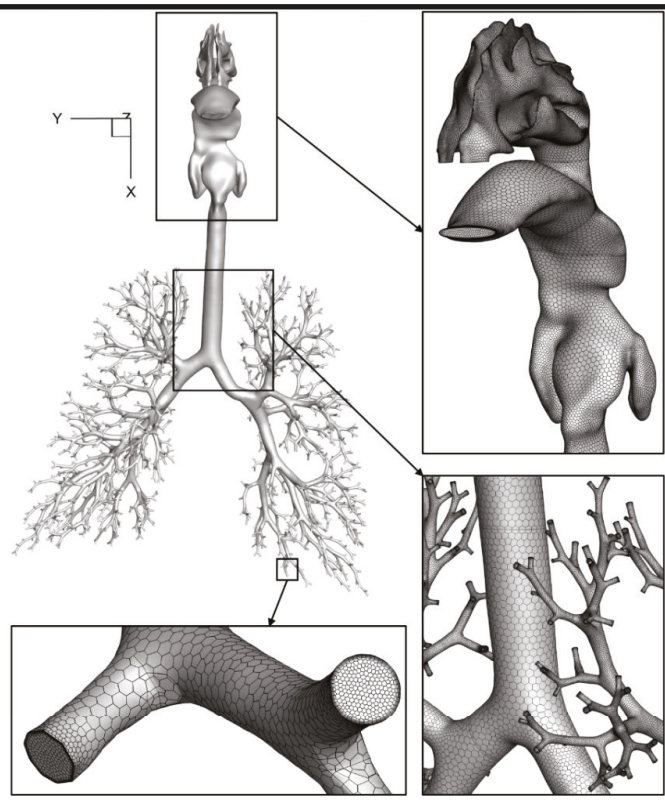

Figure 2. Geometry and polyhedral mesh with near-wall prism layers of the human respiratory system.

RESULTS AND DISCUSSION

Emitted APSDs

To evaluate the similarity between the two DPIs, Figures 3 and 4 compare the airflow velocity fields and emitted APSDs from the innovator and generic DPI with different inhalation flow rates, Q_{in}. By comparing the APSDs predicted at 30 L/min ≤ Q_{in} ≤ 90 L/min, two observations can be made. (1) In general, similar APSDs are generated using both DPIs for Q_{in} values from 30 L/min to 90 L/min, which indicates that the generic DPI has a high potential to show comparability. (2) The generic DPI, however, predicts slightly higher particle number fractions (NFs) for small particles (i.e., API), and lower NFs for large particles (i.e., carrier).

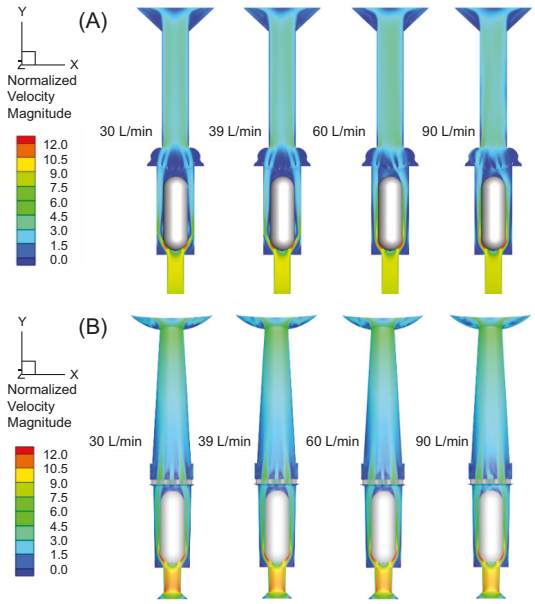

Figure 3. **Airflow patterns at midplane z = 0 in the flow channels of the two DPIs at different actuation flow rates (Q_{in} = 30, 39, 60, and 90 L/min): (A) SH, and (B) the generic DPI.**

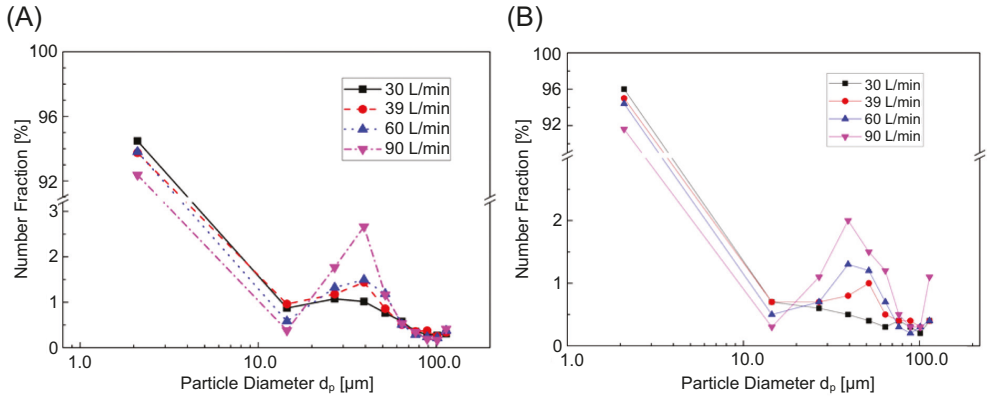

Figure 4. **Emitted APSDs from the DPIs flow channels: (A) SH, and (B) the generic DPI.**

Lung deposition

The similarity between the generic and SH DPIs in airway depositions is evaluated by comparing the carrier and API deposition distribution and their regional deposition fractions (DFs) in the 3D human respiratory system model colored by localized deposited mass [2] as shown in Figures 5(A) and (B). The API lung deposition predicted for the generic DPI agrees well with the results predicted for the SH across a range of airflow rates. Between the generic and the SH cases, the differences in regional lung DF API for all three airway regions are within 2.0% at 30 L/min ≤ Q_{in} ≤ 90 L/min.

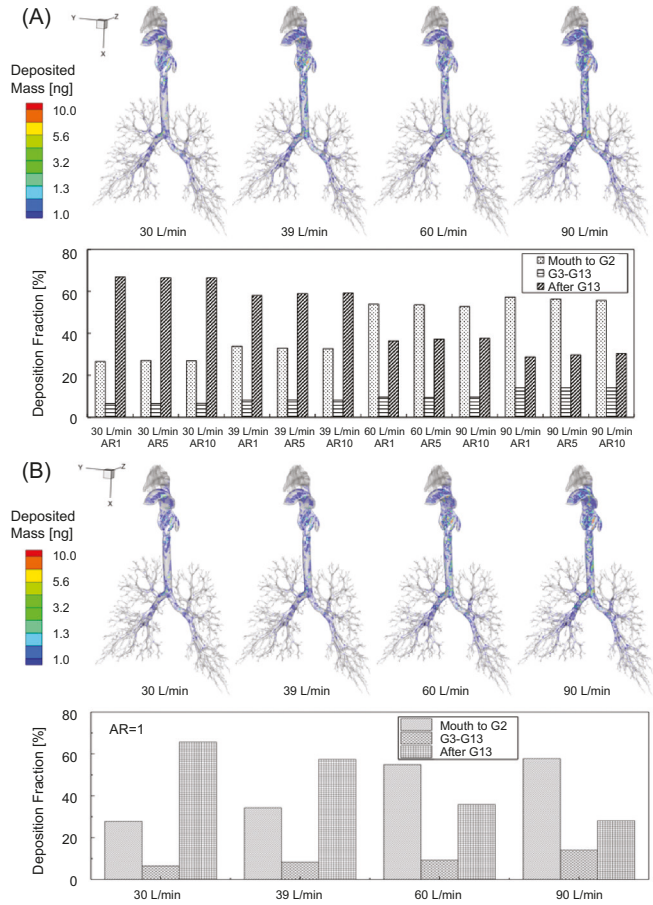

Figure 5. **Predicted sample API deposition patterns and regional deposition fractions in the human respiratory system with different carrier shapes (ARs, defined in the text) and inhalation flow rates using (A) SH DPI, and (B) the generic DPI (AR = 1).**

Overall DPI-airway drug delivery efficiency

To model the delivery efficiency to deeper airways representative of sites targeted by COPD and/or asthma treatments, overall DPI-airway drug delivery efficiency ψ is calculated (as defined in Table 1). The ψ values with different Q_{in} and carrier ARs are listed in Table 1. The results demonstrate

that low Q_{in} (i.e., 30 L/min) is favored to achieve a higher overall drug delivery efficiency using the SH DPI, and Q_{in} is the dominant factor influencing the regional API DF after G13, with the particle shape of carriers having less effect. Furthermore, the ψ comparisons between SH and the generic DPI using spherical carriers (AR = 1) demonstrate that ψ generated from the generic DPI has good agreement with the SH at inhalation flow rates from 30 to 90 L/min. Specifically, at 39 L/min $\leq Q_{in} \leq$ 90 L/min, the difference in ψ between generic and SH cases is less than 1.5% for carriers with isotropic shape. Only at the low actuation flow rate (i.e., 30 L/min), is there a slightly higher difference in ψ between two cases (5.7%) due to the relatively lower delivery efficiency of the generic DPI at Q_{in} = 90 L/min. Therefore, we concluded that the generic DPI shows satisfactory agreement with the SH DPI in terms of the general DPI-airway drug delivery efficiency.

Table 1. The overall DPI-airway drug delivery efficiencies (ψ)[a] vs. AR and Q_{in}.

SH DPI				
AR	30 L/min	39 L/min	60 L/min	90 L/min
1	65.0%	54.8%	32.9%	28.6%
5	60.7%	56.0%	32.9%	29.4%
10	64.7%	56.3%	33.7%	30.0%
Generic DPI				
AR	30 L/min	39 L/min	60 L/min	90 L/min
1	59.3%	55.2%	34.1%	28.0%

[a] $\psi = \dfrac{\text{(Deposited API after G13)}}{\text{(Total amount of API injected into the DPI)}} \times 100\% = (1 - D_{F(\text{API-DPI})})\, DF_{(\text{API-after G13})}$

CONCLUSIONS

In this study, a numerical approach has been developed based on the CFD-DEM and CFPD models and employed to predict the transport, interaction, and deposition of API and carrier particles with different shapes from the flow channels of two DPIs into a 3D human respiratory system model. DPI delivery efficiencies, emitted APSDs, and lung deposition data were obtained and compared between the two DPIs. The 'all-in-one' modeling framework developed in this study has the potential to numerically generate *in vitro*-lung deposition correlations, reduce the cost of generic product innovations, and possibly accelerate generic product review and approval.

The CFD-DEM based model in this study is a first effort at the development of an *in silico* modeling framework to understand OIDP transport dynamics in both DPIs and the human respiratory system. Although valuable insights have been gained, further work is necessary to develop a more realistic modeling strategy which considers particle transport dynamics. Specifically, the following mechanisms will be considered in the next version of this CFD-DEM modeling effort (see Figure 6):

- Particle size change dynamics due to hygroscopic growth/evaporation effects [6, 10, 16, 17] in the human respiratory tract.

- Comparability of DPIs using anisotropic shaped carriers will be further evaluated as an extension of the this study, which only evaluated the equivalence using isotropic shaped carriers (AR = 1).

- Instead of constant inhalation flow rates and static lung geometeries, patient-specific and disease-specific breathing waveforms for drug inhalation will be employed, and the physiologically realistic airway deformation kinematics will be simulated simultaneously with the particle transport from mouth/nose to alveoli [18].

- The effect of excessive secretion and/or stagnation of mucus on airflow and particle deposition in airways [19, 20] via Volume of Fluid (VOF) plus DPM [21].

- Pharmacokinetic (PK) and pharmacodynamics (PD) equivalence will be assessed by employing a CFPD-PBPK/PD modeling frameworks [9, 10, 22].

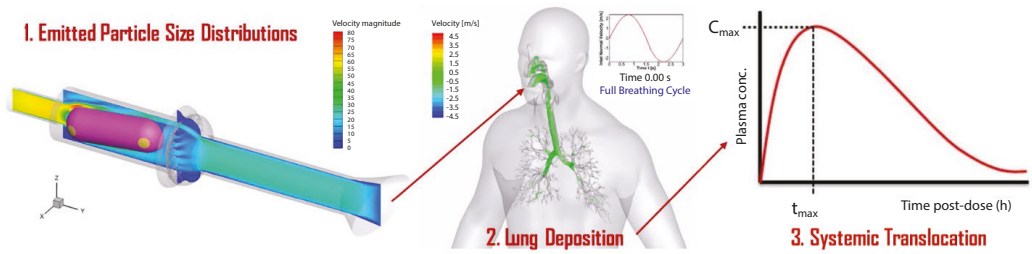

Figure 6. 'All-in-One' ***in silico*** **CFD-DEM based model for DPI comparability assessment.**

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REFERENCES

1. Delvadia RR *et al.*: In vitro tests for aerosol deposition. IV: Simulating variations in human breath profiles for realistic DPI testing. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 2016, 29(2): 196–206.

2. Zhao J *et al.*: Prediction of the carrier shape effect on particle transport, interaction and deposition in two dry powder inhalers and a mouth-to-G13 human respiratory system: A CFD-DEM study. *Journal of Aerosol Science* 2022, 160: 105899.

3. US Food and Drug Administration (2017): Guidance for Industry (Draft). Draft guidance on Tiotropium Bromide (Powder; Inhalation). Silver Spring, MD. Recommended Oct 2017.

4. Feng Y, Kleinstreuer C: Analysis of non-spherical particle transport in complex internal shear flows. *Physics of Fluids* 2013, 25(9): 091904.

5. Feng Y *et al.*: Computational transport, phase change and deposition analysis of inhaled multicomponent droplet–vapor mixtures in an idealized human upper lung model. *Journal of Aerosol Science* 2016, 96(6): 96–123.

6. Feng Y, Kleinstreuer C, Rostami A: Evaporation and condensation of multicomponent electronic cigarette droplets and conventional cigarette smoke particles in an idealized G3–G6 triple bifurcating unit. *Journal of Aerosol Science* 2015, 80: 58–74.

7. Feng Y *et al.*: Influence of wind and relative humidity on the social distancing effectiveness to prevent COVID-19 airborne transmission: A numerical study. *Journal of Aerosol Science* 2020, 105585.

8. Feng Y *et al.*: Tutorial: Understanding the transport, deposition, and translocation of particles in human respiratory systems using Computational Fluid-Particle Dynamics and Physiologically Based Toxicokinetic models. *Journal of Aerosol Science* 2021, 151: 105672.

9. Haghnegahdar A *et al.*: Computational analysis of deposition and translocation of inhaled nicotine and acrolein in the human body with e-cigarette puffing topographies. *Aerosol Science and Technology* 2018, 52(5): 483–493.

10. Haghnegahdar A, Zhao J, Feng Y: Lung aerosol dynamics of airborne influenza A virus-laden droplets and the resultant immune system responses: An *in silico* study. *Journal of Aerosol Science* 2019, 134: 34–55.

11. Zhao J *et al.*: Numerical simulation of welding fume lung dosimetry. *Journal of Aerosol Science* 2019, 135: 113–129.

12. Zhao J, Feng Y, Fromen C: Glottis motion effects on the inhaled particle transport and deposition in a subject-specific mouth-to-trachea model: An CFPD study. *Computers in Biology and Medicine* 2020, 116(9): 103532.

13. Zhao J, Feng Y, Haghnegahdar A, Sarkar S, Bharadwaj R: Numerical investigation of particle shape and actuation flow rate effects on lactose carrier delivery efficiency through a Dry Powder Inhaler (DPI) using CFD-DEM. In *AIChE Journal*, American Institute of Chemical Engineers, Annual Meeting, 2020.

14. Haghnegahdar A *et al.*: Development of a hybrid CFD-PBPK model to predict the transport of xenon gas around a human respiratory system to systemic regions. *Heliyon* 2019, 5(4): e01461–e01461.

15. Zhao J *et al.*: Influences of puff protocols and upper airway anatomy on cannabis pharmacokinetics: A CFPD-PK study. *Computers in Biology and Medicine* 2021, 132: 104333.

16. Chen X *et al.*: Numerical investigation of the interaction, transport and deposition of multi-component droplets in a simple mouth-throat model. *Journal of Aerosol Science* 2017, 105: 108–127.

17. Ferron GA *et al.*: Model of the deposition of aerosol particles in the respiratory tract of the rat. II. Hygroscopic particle deposition. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 2013, 26(2): 101–119.

18. Zhao J, Feng Y, Koshiyama K, Wu H: Prediction of airway deformation effect on pulmonary air-particle dynamics: A numerical study. *Physics of Fluids* 2021, 33(10): 101906.

19. Rajendran RR, Banerjee A: Mucus transport and distribution by steady expiration in an idealized airway geometry. *Medical Engineering & Physics* 2019, 66: 26–39.

20. Yi H, Wang Q, Feng Y: Computational analysis of obstructive disease and cough intensity effects on the mucus transport and clearance in an idealized upper airway model using the volume of fluid method. *Physics of Fluids* 2021, 33(2): 021903.

21. Farokhipour A *et al.*: 3D computational modeling of sand erosion in gas-liquid-particle multiphase annular flows in bends. *Wear* 2020, 450: 203241.

22. Haghnegahdar A, Jianan Z, Kozak M, Feng Y: Development of a Hybrid CFD-PBPK Model to Predict the Transport and Translocation of Xenon Gas from a Subject-Specific Human Respiratory System to Systemic Regions. *Heliyon* 2019, 5(4): e01461.

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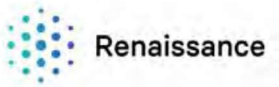

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