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PREDICTING INHALED DRUG DEPOSITION USING PARTICLE AERODYNAMICS, DEVICE RESISTANCE, AND INSPIRATORY FLOW

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ABSTRACT

Inhaled drug delivery is central to treating respiratory diseases because it can place therapy near the intended pulmonary site of action. However, predictable lung deposition remains difficult because particle properties, device performance, and patient breathing behavior interact in non-linear ways. Current development workflows often treat in-vitro aerosol testing and in-vivo imaging as separate sources of evidence. This separation limits the ability to forecast regional deposition from the combined effects of formulation, device, and patient variables. The objective is to develop a machine learning model that predicts regional lung deposition of inhaled drugs. The model is designed to integrate particle aerodynamic parameters, device resistance characteristics, and patient inspiratory flow profiles. A gradient-boosted regression model is conceptually trained on combined cascade impaction outputs, device resistance descriptors, inspiratory flow waveforms, and deposition fractions from imaging or computational simulations. The model outputs predicted deposition for clinically relevant lung regions. Conceptually, the model could forecast the fine-particle dose reaching the central and peripheral airways for a given patient profile and inhalation device. It could also identify whether particle size, device resistance, or inspiratory flow is expected to dominate the deposition outcome. Such a model could accelerate inhaled product development by supporting virtual bioequivalence assessment and personalized device–formulation selection. It would provide a structured bridge between aerosol characterization, patient physiology, and regional lung delivery.

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Introduction

Inhaled drug delivery offers therapeutic advantages by directing medication toward the respiratory tract while potentially limiting systemic exposure, but deposition remains variable across patients and products. Whole-lung and regional modeling studies show that local dose delivery depends on the interaction between airway geometry and aerosol transport behavior [1]. Patient-specific airway models further indicate that deposition predictions can change when anatomical and flow-related characteristics are represented more explicitly [2]. Therefore, reliable prediction requires a model structure that treats lung deposition as the result of coupled formulation, device, and patient processes rather than as a fixed product attribute.

Current inhaled product development relies heavily on in-vitro aerodynamic characterization, while in-vivo imaging and computational fluid dynamics provide complementary but less routinely available evidence. Real-time particle emission monitoring has been proposed as a non-invasive way to connect dry powder inhaler performance with site-specific deposition expectations [3]. Imaging-informed and simulation-informed approaches have also been used to estimate deposition from respiratory anatomy and inhalation behavior [4, 5]. However, the practical gap remains that cascade impaction, device testing, patient flow assessment, and regional deposition imaging are often not integrated into a single predictive framework.

Machine learning provides a way to combine tabular device and formulation descriptors with simulation-derived or imaging-derived deposition labels. Multi-output learning has been explored for predicting deposition across airway regions, suggesting

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that deposition can be framed as a structured prediction problem rather than a single aggregate endpoint [6]. Hybrid computational approaches that combine discrete particle modeling with machine learning further support the idea that complex aerosol transport patterns can be approximated for faster prediction [7]. Such approaches are particularly relevant when model inputs include particle size metrics, device resistance, and patient flow variables that may interact in ways not captured by simple empirical equations.

This manuscript proposes a conceptual predictive model for inhaled drug deposition that uses aerodynamic, device, and inspiratory flow inputs to estimate regional lung delivery. Prior work on inspiratory flow and dry powder inhaler performance shows that the patient–device interaction can strongly influence emitted dose and lung delivery potential [8]. Studies of peak inspiratory flow in asthma and chronic obstructive pulmonary disease also indicate that device-specific resistance should be represented directly rather than treated as a background condition [9, 10]. A machine learning model built around these principles could support more rational formulation design, device selection, and patient-centered inhaled therapy development.

Background

Mechanisms of Aerosol Deposition in the Respiratory Tract

Aerosol deposition in the respiratory tract is governed mainly by inertial impaction, gravitational sedimentation, and Brownian diffusion. Larger or faster-moving particles are more likely to deposit in the oropharynx and central airways by impaction, while smaller particles can penetrate more deeply and deposit through sedimentation or diffusion depending on residence time. Computational models of regional aerosol deposition have emphasized that airway branching, local flow fields, and particle behavior jointly determine where inhaled material is retained. Deep-lung simulation methods further suggest that a predictive model should represent both proximal airway losses and peripheral transport processes when estimating regional deposition.

Particle Aerodynamics and In-Vitro Characterization

Particle aerodynamic behavior is commonly summarized through mass median aerodynamic diameter, geometric spread, emitted dose, and fine-particle fraction. These descriptors are obtained from in-vitro aerosol characterization and are useful because they translate formulation properties into deposition-relevant transport features. In silico optimization of non-spherical aerosols shows that particle shape and aerodynamic behavior can alter targeting across the respiratory tract [11]. Computational assessments of mouth–throat effects also indicate that aerodynamic properties should be interpreted together with upper-airway losses before inferring the fraction likely to reach the lower lung.

Inhaler Device Resistance and Inspiratory Flow

Inhaler devices impose different resistance profiles, and these profiles determine how a patient's inspiratory effort is converted into airflow through the device. Dry powder inhalers are especially dependent on inspiratory flow because powder deaggregation and emitted aerosol quality are driven by the energy supplied during inhalation [8]. Clinical studies comparing inhaler resistance conditions show that patients may generate different peak inspiratory flows depending on the device used [9]. For soft mist inhalers and other device classes, in-vitro and in-silico analyses also suggest that device-specific aerosol generation should be modeled alongside breathing behavior [12].

Patient Factors Affecting Deposition

Patient factors such as airway caliber, disease state, inhalation effort, and age-related respiratory mechanics can change deposition even when the same product is used. Chronic obstructive pulmonary disease can alter both airway geometry and inspiratory flow capacity, making regional delivery different from that expected in healthy lungs [13]. Measurements of peak inspiratory flow in chronic obstructive pulmonary disease patients highlight that some users may not achieve an inhalation pattern that is optimal for specific dry powder inhalers [14]. These findings support including disease state, spirometric impairment, and inspiratory maneuver descriptors as explicit features in deposition prediction.

Machine Learning and CFD in Pulmonary Drug Delivery

Machine learning and computational fluid dynamics have increasingly been used to approximate respiratory aerosol transport, especially when direct imaging evidence is limited. A machine learning model for aerosol transport through multiple airway generations illustrates how deposition behavior can be learned from simulated respiratory tract data [15]. CFD-based in-silico modeling has also been discussed as a way to establish links between laboratory aerosol measurements and in-vivo respiratory tract deposition [16]. The remaining need is an integrated model that combines formulation aerodynamics, device resistance, inspiratory flow, and patient features into one clinically interpretable prediction pipeline.

Model Development Overview

High-Level Prediction Pipeline

The proposed prediction pipeline begins with a formulation–device–patient feature vector assembled from particle sizing data, device resistance measurements, and patient inspiratory flow descriptors. The output is a set of predicted deposition fractions for the oropharynx, central airways, and peripheral lung, reflecting the multi-region nature of inhaled delivery. Whole-lung modeling approaches support this regional framing because they estimate locally delivered dose rather than only total lung

dose [1]. Patient-specific simulation studies also show that realistic airway structures and inhalation profiles can be incorporated into deposition prediction workflows [17].

Figure 1 presents the proposed predictive architecture for integrating particle aerodynamics, inhaler-device resistance, patient inspiratory-flow behavior, and deposition evidence into interpretable regional lung-deposition forecasts.

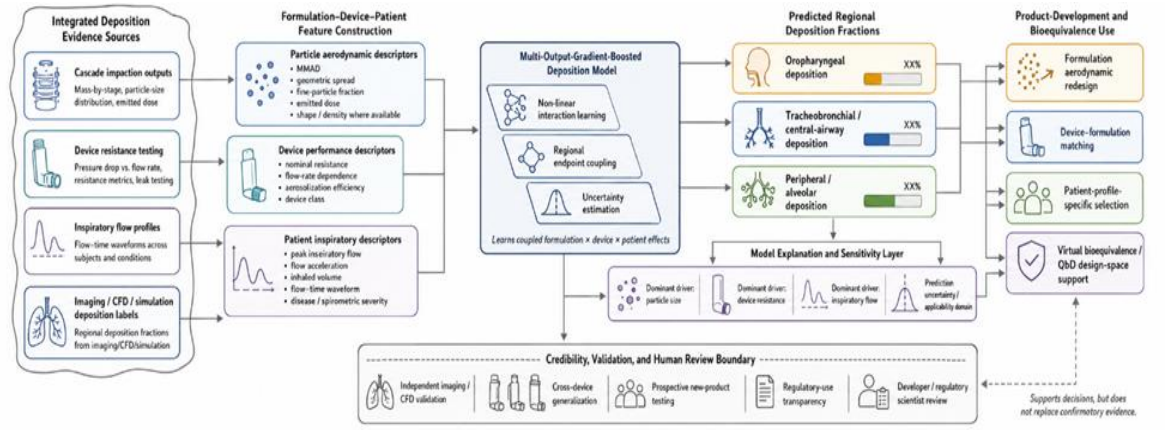

Figure 1. Predictive architecture for regional inhaled drug deposition using aerodynamic, device, and inspiratory-flow inputs.

Core Input Features

Core aerodynamic inputs include mass median aerodynamic diameter, geometric spread, fine-particle fraction, and emitted dose, while device inputs include resistance and flow-rate dependence. Patient inputs include peak inspiratory flow, inhalation volume, flow acceleration, age category, disease state, and spirometric severity where available. Studies of inhaler usability and inspiratory profiles show that device handling and inhalation dynamics can be captured as clinically meaningful descriptors [18]. Pooled analyses of dry powder inhaler use further support encoding whether a patient can generate sufficient inspiratory flow through a specific device class [19].

Design Principles

The model should use multi-output regression because regional deposition fractions are related outputs rather than independent endpoints. It should also include uncertainty quantification so that predictions can be interpreted as decision-support evidence rather than absolute measurements. Image-based deposition prediction using statistical shape models and convolutional neural networks illustrates the value of combining anatomical representation with predictive modeling [5]. Rapid deposition analysis methods similarly suggest that computationally efficient prediction is important if the model is to be useful during iterative product development [4].

Data Sources and Feature Engineering

Compiling a Deposition Dataset

A deposition dataset would be compiled by pairing regional deposition fractions from in-vivo scintigraphy, SPECT, computational fluid dynamics, and internal development simulations with their corresponding aerosol and flow inputs. Benchmark respiratory deposition cases can provide harmonized simulation evidence for model training and comparison when in-vivo data are sparse. Validated respiratory deposition predictions from medical images also suggest that imaging-derived anatomy and simulation outputs can be structured into reusable predictive datasets [5]. Systematic reviews of in-silico bioequivalence modeling indicate that the credibility of such datasets depends on transparent links between model assumptions, validation evidence, and intended regulatory use [20].

Encoding Aerodynamic Size and Device Features

Cascade impaction profiles can be reduced to summary variables such as mass median aerodynamic diameter, geometric spread, fine-particle fraction, and emitted dose. Device resistance can be encoded as a single nominal value when only limited information is available, or as a flow-rate-dependent curve when richer device testing data exist. Studies of dry powder inhaler deposition and CFD validation show that device-generated aerosol properties must be connected with airway transport conditions to support credible prediction [21]. Real-time particle emission monitoring also indicates that dynamic aerosol release signals could be transformed into deposition-relevant features for dry powder inhaler models [22].

Representing Inspiratory Flow and Patient Variables

Inspiratory flow can be represented using peak inspiratory flow, inhalation ramp rate, inhaled volume, and simplified flow-time curve descriptors. Disease severity can be encoded through spirometry measures and categorical disease labels, while missing values can be handled using disease-specific typical profiles rather than arbitrary constants. Clinical work on

suboptimal daily peak inspiratory flow shows that patient technique and respiratory disease status can meaningfully affect dry powder inhaler use [23]. Additional studies on suboptimal peak inspiratory flow in chronic obstructive pulmonary disease support treating flow capacity as a patient-specific predictor rather than a fixed assumption [24].

Table 1 organizes the proposed model inputs according to their mechanistic relevance for regional lung-deposition prediction and their expected role in formulation, device, and patient-level decision-making.

Table 1. Feature-to-deposition logic for regional inhaled drug delivery prediction

Input domain	Representative variables	Deposition mechanism represented	Expected regional influence	Development interpretation	Key modeling consideration
Particle aerodynamic size	Mass median aerodynamic diameter, aerodynamic size distribution, geometric standard deviation	Determines likelihood of impaction, sedimentation, and deep-lung penetration	Larger aerodynamic size may increase oropharyngeal and central-airway deposition; smaller respirable fraction may support peripheral delivery	Guides particle-size optimization and formulation redesign	Avoid reducing the aerosol to a single size metric when polydispersity is important
Fine-particle and emitted-dose performance	Fine-particle fraction, emitted dose, respirable dose, retained device dose	Represents the fraction of drug leaving the device in a potentially lung-reachable form	Higher respirable output may increase lower-airway availability if upper-airway losses remain controlled	Supports comparison of formulation batches and device–formulation combinations	Model should distinguish emitted dose from regionally deposited dose
Particle morphology and density	Shape, density, hygroscopic behavior, agglomeration tendency where available	Modifies aerodynamic behavior after aerosol generation	May alter transport through mouth–throat, central, and peripheral regions despite similar nominal size	Helps interpret why formulations with similar MMAD may behave differently	Missing morphology data may limit applicability for complex or non-spherical aerosols
Device resistance	Nominal resistance, resistance category, pressure–flow relationship	Converts patient inspiratory effort into device airflow and aerosolization energy	Higher resistance may reduce achievable flow in some patients but improve powder deaggregation in others	Enables rational device selection for target populations	Resistance should interact with flow variables rather than be treated as an isolated covariate
Device aerosolization behavior	Flow-rate dependence, powder deaggregation efficiency, device class, plume or aerosol-generation profile	Determines quality and timing of aerosol emission during inhalation	Can shift deposition by changing emitted particle cloud characteristics and lung-entry timing	Supports device redesign and device–formulation matching	Device descriptors should be aligned to the same flow condition used for patient simulation
Inspiratory-flow magnitude	Peak inspiratory flow, mean inspiratory flow, flow through device	Captures the driving force for aerosol generation and airway transport	Higher flow may increase impaction proximally while also improving powder dispersion for some DPIs	Identifies patients unlikely to generate adequate device-specific flow	Peak flow alone may miss clinically important waveform differences
Inspiratory-flow dynamics	Flow acceleration, inhaled volume, inhalation duration, flow–time curve shape	Represents timing, residence time, and aerosol delivery synchronization	Slower or prolonged inhalation may favor deeper transport for some aerosol profiles; rapid acceleration may increase proximal losses	Supports patient-technique guidance and personalized device matching	Waveform features may be more informative than single summary measures
Patient respiratory status	Disease label, spirometric severity, airway obstruction proxy, age or lung-size category	Represents anatomical and physiological modifiers of aerosol transport	Obstructive disease may shift deposition toward narrowed or proximal airways; age and lung size may alter regional distribution	Enables disease-specific product-development scenarios	Disease variables should not substitute for direct airway or flow evidence when available
Deposition labels	Scintigraphy, SPECT, CFD-derived regional	Provides target outcomes for supervised regional prediction	Defines oropharyngeal, tracheobronchial, and peripheral deposition endpoints	Connects in-vitro aerosol evidence with in-vivo or simulation-	Label provenance should be tracked because imaging, CFD, and

fractions, simulation benchmarks		supported lung delivery	simulation labels differ in uncertainty

Predictive Model Architecture

Model Choice – Gradient-Boosted Trees

Gradient-boosted trees are a suitable conceptual choice because inhaled deposition prediction is primarily a tabular, multi-factor regression problem involving aerodynamic, device, and patient variables. Such models can capture non-linear interactions without requiring the manuscript to assume experimental results or fixed performance metrics. Multi-output machine learning approaches for airway deposition prediction support the feasibility of estimating several regional deposition endpoints from shared input features [6]. Hybrid machine learning and particle-modeling studies also suggest that learned approximations can complement mechanistic aerosol transport simulations [7].

Input Feature Vector and Pre-processing

The input feature vector should include normalized aerodynamic measures, encoded device resistance descriptors, and patient inspiratory flow variables aligned to the same inhalation condition. Missing patient data can be imputed using disease-informed typical values, while skewed variables such as fine-particle fraction or aerodynamic diameter can be transformed to reduce instability in model fitting. Studies of inspiratory flow through different dry powder inhalers show that resistance and patient effort are not interchangeable and should be processed as separate but interacting inputs [25]. Inappropriate peak inspiratory flow in chronic obstructive pulmonary disease further supports pre-processing strategies that preserve clinically meaningful flow categories [14].

Output: Regional Deposition Fractions

The model output is a vector of predicted regional deposition fractions for the oropharyngeal, tracheobronchial, and alveolar regions, accompanied by uncertainty intervals for decision support. These outputs should be interpreted conceptually as expected deposition tendencies under a specified formulation, device, and patient profile rather than as direct clinical measurements. Simulations of realistic dosages in patient-specific airways demonstrate why multi-region outputs are more informative than a single total lung deposition estimate [2]. Efficient deep-lung computational methods also support representing peripheral deposition separately from upper-airway and central-airway losses.

Handling Inter-Patient Variability and Disease-Specific Factors

Accounting for Disease-Induced Changes in Airway Geometry

Disease-induced changes in airway geometry can be represented through categorical disease labels, spirometric descriptors, and anatomy-derived modifiers when imaging or simulation data are available. Chronic obstructive pulmonary disease may narrow or distort conducting airways, which would be expected to shift deposition toward more proximal regions under some inhalation conditions [13]. Whole-lung and patient-specific simulation frameworks support the idea that anatomical variation should be treated as a determinant of locally delivered dose rather than as residual noise [1, 2]. In the proposed model, disease features could therefore allow the algorithm to learn disease-specific offsets in regional deposition patterns without requiring separate models for every patient subgroup.

Personalizing Flow Profiles

A personalized flow representation should extend beyond peak inspiratory flow by including acceleration, inhaled volume, and the shape of the flow-time curve. Clinical studies of dry powder inhaler use show that patients generate different inspiratory flows across device resistances, meaning that a single flow value may not capture the full patient–device interaction [11, 25]. Real-time particle emission monitoring also suggests that dynamic inhalation and aerosol release behavior can provide deposition-relevant information during dry powder inhaler use [3, 22]. A model that accepts simplified waveform features would be expected to better represent powder deaggregation, emitted dose formation, and regional lung entry than one relying only on a peak value.

Table 2 shows the key inspiratory flow characteristics that influence dry powder inhaler performance and highlights why considering features beyond peak flow can improve patient–device interaction modeling.

Table 2. Key Inspiratory flow features affecting dry powder inhaler performance

Feature	Description	Clinical Relevance
Peak Inspiratory Flow (PIF)	Maximum flow rate achieved during inhalation	Often used as a standard measure of inhalation effort but may not capture full device–patient interaction
Flow Acceleration	Rate of increase in flow at the start of inhalation	Influences powder deaggregation and initial aerosol formation
Inhaled Volume	Total volume of air inhaled through the device	Affects dose delivery to different lung regions

Flow-Time Curve Shape	Overall temporal pattern of the inspiratory flow	Captures dynamic behavior relevant for deposition and emitted dose formation

Sensitivity to Age and Lung Maturation

Age-related differences in airway caliber, inhaled volume, and breathing pattern can influence regional deposition, especially when pediatric or older populations are considered. Imaging-based and statistical-shape approaches indicate that anatomical scaling can be incorporated into respiratory deposition prediction workflows when patient-specific imaging is not available [5]. Machine learning models trained on simulated airway transport data could use age or lung-size scaling factors as structured features rather than treating age as a purely demographic covariate [15]. This approach would allow the model to generalize conceptually across maturation states while preserving the need for external evaluation in clinically relevant age groups.

Model Interpretability and Device-Formulation Design Guidance

Explaining Deposition Predictions to Product Developers

Model interpretability is essential because deposition predictions are intended to guide formulation and device decisions rather than simply produce opaque numerical outputs. Feature-attribution methods such as SHAP could rank the relative influence of mass median aerodynamic diameter, fine-particle fraction, device resistance, and inspiratory flow on each regional deposition prediction. Prior work on dry powder inhaler flow dependence supports the expectation that resistance and inspiratory effort may dominate emitted aerosol behavior in some device contexts [8], while particle-shape and aerodynamic optimization studies show that particle properties can strongly affect regional targeting [11]. Interpretable outputs would help developers understand whether a predicted deposition pattern is driven mainly by formulation design, device selection, or patient inhalation behavior.

From Prediction to Design Choices

A predictive model could be used to virtually compare candidate formulations and inhaler devices before committing to costly in-vivo imaging studies. For example, CFD-validated airway deposition studies suggest that changes in device-generated aerosol properties can alter airway deposition expectations [21], while in-vitro and in-silico soft mist inhaler analyses show how device format can be evaluated in relation to lung deposition potential [12]. The model could therefore screen whether a formulation with a different aerodynamic profile or a device with altered resistance would be expected to improve peripheral delivery for a target patient group. Such use would frame prediction as design guidance, not as a replacement for clinical confirmation.

Integration Into Inhaled Product Development And Regulatory Submissions

Supporting Bioequivalence and Bridging Studies

Inhaled product bioequivalence often depends on whether a changed formulation or device produces comparable lung delivery at clinically relevant sites. A predictive deposition model could support bridging arguments by estimating whether regional deposition would be expected to remain similar after changes in aerodynamic size distribution, emitted dose, or device resistance. Systematic evaluation of modeling and simulation for inhaled bioequivalence highlights both the potential value and the need for careful credibility assessment of such approaches [20]. CFD-based in-vitro to in-vivo correlation frameworks also support using mechanistic simulations as part of an evidence package linking aerosol measurements with respiratory deposition [16].

Embedding in QbD Workflows

Within a quality-by-design workflow, the model could define a design space in which aerodynamic properties, device resistance, and inspiratory flow conditions are expected to produce acceptable regional deposition. Aerosol transport benchmarks and in-silico method comparisons show that standardized simulation cases can help define model behavior and reveal uncertainty in deposition predictions. Deep-lung modeling methods further suggest that peripheral deposition can be treated as a specific target during formulation and device optimization. By mapping how formulation and device variables influence predicted deposition, the model could support rational selection of development ranges rather than relying only on post hoc product testing.

Evaluation Strategy

Deposition Prediction Accuracy

Evaluation should compare predicted regional deposition patterns with independent in-vivo imaging or validated simulation outputs without presenting the model as experimentally proven in this conceptual manuscript. Metrics such as mean absolute error could be used during development to summarize deviations in each lung region, but their interpretation should remain tied to clinical and biopharmaceutical relevance rather than isolated statistical performance. Rapid deposition analysis and validated image-based prediction studies provide examples of how model outputs can be compared with anatomically informed deposition evidence [4, 5]. The evaluation should therefore assess whether predictions are directionally and regionally credible for the intended product-development decision.

Generalization across Devices and Formulations

Generalization should be assessed by applying the model to drug–device combinations that differ from those used during model fitting. Studies of inspiratory flow profiles across inhaler devices indicate that device resistance can alter how patient effort translates into aerosol performance [18, 19], making cross-device testing essential. Work on lung deposition using different inhalation devices also suggests that resistance and device format should be evaluated as interacting factors rather than isolated descriptors [13]. A robust model would be expected to preserve plausible deposition predictions when exposed to new combinations of formulation aerodynamics, device resistance, and patient inspiratory profiles.

Prospective Prediction for a New Inhaled Product

A prospective evaluation strategy would use the model to forecast deposition for a newly developed inhaled formulation before imaging data are available, then compare predictions with subsequent scintigraphy, SPECT, or validated simulation evidence. In-silico assessment of upper-airway effects shows that mouth–throat deposition can materially affect the dose available to the lower lung, so prospective testing should include both proximal losses and distal regional delivery. Multi-output airway deposition models also support evaluating several deposition regions simultaneously rather than relying on total lung dose alone [6]. This prospective framework would test whether the model can inform development decisions before confirmatory evidence is generated.

Table 3 defines how the proposed deposition model should be evaluated for predictive credibility, cross-device generalization, interpretability, and decision-use readiness in inhaled product development.

Table 3. Model evaluation and decision-use framework for inhaled deposition prediction

Evaluation dimension	Primary question	Suggested evaluation approach	Evidence needed	Decision-use implication	Main risk if neglected
Regional prediction accuracy	Does the model estimate deposition fractions credibly for each lung region?	Compare predicted oropharyngeal, tracheobronchial, and peripheral fractions with independent imaging or validated simulation evidence	Scintigraphy, SPECT, CFD, or benchmark simulation labels not used in model training	Supports use of the model as a regional-deposition forecasting tool	A model may appear accurate for total lung dose while misrepresenting clinically important regional distribution
Multi-output consistency	Are regional deposition outputs physiologically coherent when considered together?	Assess whether predicted regional fractions follow plausible mass-balance and deposition-pattern relationships	Region-level outcome vectors and expected deposition constraints	Strengthens interpretation of deposition as a linked regional process	Independent region predictions may produce internally inconsistent deposition patterns
Cross-device generalization	Does performance persist across inhalers with different resistance and aerosolization behavior?	Test the model on device classes or resistance profiles excluded from training	Independent device-resistance and aerosol-performance datasets	Supports device–formulation comparison and device-switch scenarios	The model may overfit to one inhaler class and fail for new device formats
Cross-formulation generalization	Can the model handle new aerodynamic profiles and formulation designs?	Evaluate candidate formulations with particle-size distributions or emitted-dose profiles outside the training center	New formulation batches, alternative particle-engineering approaches, or simulated formulation variants	Supports early formulation screening and QbD design-space exploration	Predictions may be unreliable for formulations with unfamiliar morphology, hygroscopicity, or dispersion behavior
Patient-profile generalization	Are predictions stable across disease severity, inspiratory capacity, age, and lung-size groups?	Stratify error by COPD, asthma, healthy reference profiles, pediatric or older-adult proxies where available	Patient-flow profiles, spirometry, disease labels, and anatomical modifiers	Enables patient-centered device–formulation selection	Average performance may hide poor prediction for patients with limited inspiratory capacity
Uncertainty and applicability domain	Does the model indicate when a prediction is uncertain or outside familiar input space?	Add prediction intervals, distance-to-training-domain checks, and warning flags for sparse input regions	Training-domain summaries, feature-distribution boundaries, uncertainty calibration evidence	Prevents overconfident use in unsupported product or patient scenarios	Users may treat speculative predictions as confirmatory evidence

Interpretability of drivers	Can users identify whether deposition is driven mainly by formulation, device, or patient factors?	Use feature-attribution methods by region and scenario, such as SHAP-style driver ranking	Input features linked to each predicted regional output	Helps developers decide whether to redesign particles, change device resistance, or target patient technique	Black-box predictions may not translate into actionable development decisions
Prospective development utility	Does the model improve decisions before confirmatory imaging or simulation results are available?	Forecast deposition for a new product, then compare predictions with later imaging, CFD, or validated simulation evidence	Time-stamped prospective predictions and later confirmatory deposition evidence	Tests whether the model can support real product-development decisions	Retrospective fit may not translate into useful forward-looking guidance
Regulatory and bioequivalence relevance	Can model outputs support a transparent evidence package for bridging or virtual bioequivalence?	Document assumptions, validation evidence, sensitivity analyses, uncertainty, and intended context of use	Model documentation, validation reports, scenario analyses, and human-review records	Positions the model as supportive evidence rather than a replacement for required confirmation	Unsupported regulatory claims may exceed the model's credibility and intended use
Human-review integration	Are model outputs reviewed by formulation, device, clinical, and regulatory experts before action?	Embed prediction review into development meetings, QbD assessment, and bioequivalence planning	Review logs, decision rationales, and expert sign-off	Ensures predictions are interpreted alongside mechanistic and experimental evidence	Automated outputs may be used without adequate scientific judgment

Limitations

Limited In-Vivo Data Availability

High-quality in-vivo deposition imaging data are limited, heterogeneous, and often difficult to pair with complete formulation, device, and inspiratory-flow descriptors. As a result, the model may need to rely substantially on CFD-generated or simulation-derived labels, which can expand coverage but may not fully reproduce in-vivo airway motion, mucus conditions, or patient technique. Reviews of CFD-based in-silico modeling emphasize that credibility depends on validation against relevant respiratory deposition evidence [16]. Systematic assessment of inhaled bioequivalence modeling likewise indicates that regulatory usefulness requires transparent assumptions, defined applicability domains, and careful comparison with experimental or clinical data [20].

Simplifying Assumptions in Aerodynamic Features

The proposed model uses bulk aerodynamic descriptors such as mass median aerodynamic diameter, geometric spread, and fine-particle fraction, but these variables may not fully describe polydisperse aerosol dynamics. Hygroscopic growth, particle shape, density, agglomeration, and local humidity conditions can influence deposition after aerosol generation, and simplified feature engineering may underrepresent these effects. In-silico optimization of fiber-shaped aerosols shows that particle morphology can change targeting behavior across the respiratory tract [11]. Mouth–throat and regional airway simulations further indicate that patient-specific geometry and upper-airway losses can modify the meaning of aerodynamic summary metrics.

Conclusion

The proposed predictive model integrates particle aerodynamics, inhaler device resistance, and patient inspiratory flow to estimate regional lung deposition of inhaled drugs. It frames deposition as a multi-output prediction problem in which oropharyngeal, central-airway, and peripheral-lung delivery are linked but distinct outputs.

A key strength of the model is its ability to combine multi-source evidence into a single development-oriented framework. By providing interpretable feature contributions, it could help developers understand whether deposition behavior is mainly influenced by formulation properties, device resistance, or patient breathing characteristics.

Important challenges remain before such a model could be used with confidence in product development or regulatory decision-making. Sparse in-vivo deposition data, reliance on simulated training labels, and uncertainty around regulatory acceptance of in-silico evidence all require careful prospective evaluation.

Future progress will depend on collaborative generation of open, well-annotated deposition datasets that connect aerosol characterization, device properties, inspiratory flow, lung geometry, and regional deposition outcomes. Prospective validation in clinical imaging studies would be essential to establish when model predictions are sufficiently credible for formulation design, device selection, and virtual bioequivalence support.

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