molecular pharmaceutics

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Perspective

iBCS: 4. Application of the Inhalation Biopharmaceutics Classification System to the Development of Orally Inhaled Drug Products

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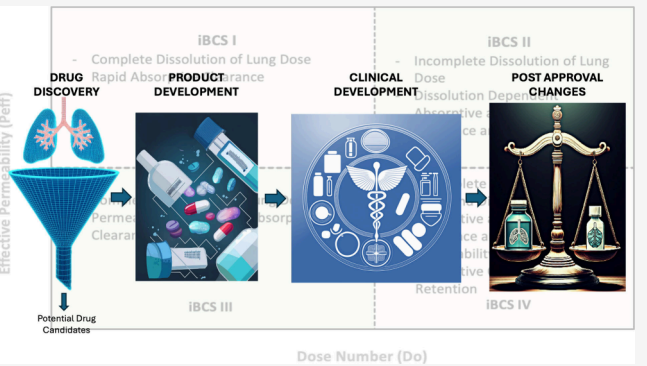
Cite This: *Mol. Pharmaceutics* 2025, 22, 1740−1751

ABSTRACT: This is the fourth paper in a series describing an inhalation biopharmaceutics classification system (iBCS), an initiative supported by the Product Quality Research Institute. The paper examines the application of the inhalation Biopharmaceutics Classification System (iBCS) through the drug discovery, development, and postapproval phases for orally inhaled drug products (OIDP) and for the development of generic OIDPs. We consider the implication of the iBCS class in terms of product performance and identify the practical gaps that must be filled to enable the classification system to be adopted into day-to-day practice. Consideration is given to the critical experimental data required and the methods for their generation with a focus on: (i) dose to the lungs, (ii) drug solubility in relevant media and methods to model the dissolution of respirable formulations, and (iii) pulmonary drug permeability. As described in three prior publications, the iBCS was developed to classify inhaled drugs based on physicochemical and biorelevant product attributes in a manner that will allow formulators and discovery chemists to identify and mitigate product development risks. It was not established to enable *in vitro* determination of bioequivalence between orally inhaled drug products. However, once analytical methods are in place to correctly classify inhaled drugs, the system has the potential to provide an understanding of the development risks associated with both establishing bioequivalence between two drug products and enabling postapproval changes based on product iBCS class.



KEYWORDS: *Inhalation-based Biopharmaceutics Classification System (iBCS), Orally Inhaled Drug Products, Dose Number, Solubility, Permeability, Dissolution, Pulmonary Drug Delivery, Bioequivalence*

1. INTRODUCTION

The inhalation Biopharmaceutics Classification System (iBCS) has been developed as a decision-making tool to derisk inhaled product development for drug discovery chemists and formulators.[1−3] The iBCS is a framework based on scientific principles that can aid in lead drug candidate optimization; be used to mitigate risk during translation between preclinical to clinical phases of drug development and inform formulation or device choices or changes thereto. The iBCS was not developed to determine or assign bioequivalence for orally inhaled drug products (OIDPs), but with further development and integration into regulatory decision-making, the iBCS class of an OIDP can inform our understanding of the challenges associated with achieving bioequivalence as well as the effects of postapproval changes.

As the iBCS is based on dose, solubility, and permeability, it requires experimental methods that are robust, reliable, and discriminating for differences in these properties that are relevant for clinical drug exposure. Drug bioavailability is derived from the exposure of lung tissue to the drug for locally acting inhaled products or systemic availability for nonlung targeted drugs. The class boundaries, based on dose number and permeability, have been determined using mechanistic modeling to identify "break points" where bioavailability and rate of absorption are dependent on these properties. Widespread application of the iBCS will require the development of *in vitro* methods for measuring lung dose, solubility, and permeability

Received: December 28, 2024
Revised: February 26, 2025
Accepted: March 1, 2025
Published: March 13, 2025

https://doi.org/10.1021/acs.molpharmaceut.4c01534
Mol. Pharmaceutics 2025, 22, 1740−1751

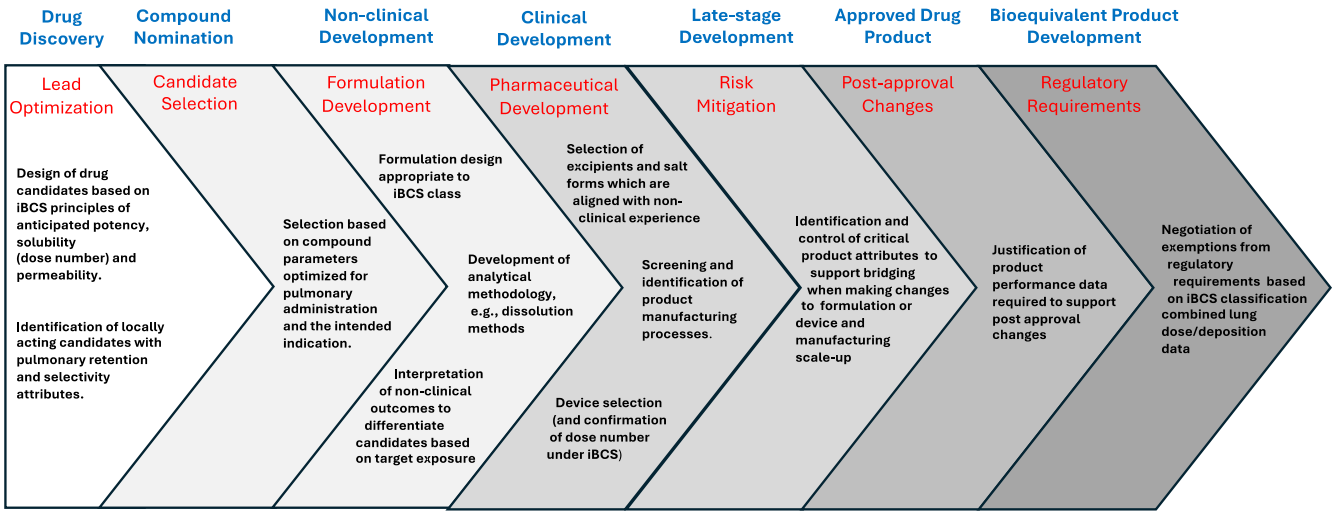


Figure 1. Inhalation Biopharmaceutics Classification System (iBCS) framework has a wide range of applications through the drug discovery, development, and postapproval phases for new small molecule OIDPs and for the development of generic OIDPs. Applications include optimization and selection of the most suitable iBCS class drug for a particular target, informing risk mitigation for pharmaceutical development during nonclinical and clinical development stages, and justifying data requirements for postapproval stages and demonstration of bioequivalence.

that possess sufficient accuracy and reproducibility to assign products to the correct iBCS class, as well as methods to characterize formulation dissolution rate for products where this is a critical product attribute.

In this paper, we consider the use of iBCS in the various phases of inhaled drug discovery and development and evaluate the implications of iBCS class for critical product attributes. Looking forward, we consider the methodological developments and generation of data that will be required to expand the evidence that underpins the iBCS framework. These methods are essential to enable full application of the iBCS in product development and realize the potential for future incorporation into regulatory frameworks for the development of OIDPs.

2. APPLICATION OF THE IBCS

Once drug and drug product characterization methodologies to support the iBCS have been developed and validated, OIDPs can be classified based on the API molecular properties (solubility and permeability) and drug product characteristics (dose) and controlled by class-appropriate testing (dissolution). The iBCS class designation of an inhaled drug has different applications and implications at each stage, as a new molecule moves through the drug discovery and development process (Figure 1).

As pulmonary retention (slow absorption from the lung into the systemic circulation) is desired for locally acting inhalation drugs, the iBCS can be applied in drug discovery and early stage development to identify the best inhaled drug candidates for development based on the iBCS attributes of solubility and anticipated potency (the determinants of dose number) and permeability. In contrast, Class I properties will have advantages for a systemically acting drug, for which a fast systemic absorption is desired. The iBCS class may also alert the discovery scientist to aspects that need to be controlled or at least noted during the design of decision-making experiments for drug candidate nomination and selection. For example, an iBCS Class I molecule with a target in the lungs will benefit from a lung retentive mechanism, *e.g.* tissue binding, cellular drug trapping, long receptor occupancy, or require formulation approaches such as use of liposomes[4] to avoid rapid clearance from the site of action.

For a drug with low solubility and dissolution rate limited bioavailability (iBCS Class II or IV) it may be necessary to carefully control the amorphous content and/or presence of polymorphic crystal forms in formulations to control the impact of dissolution on lung bioavailability in both preclinical and clinical development. In addition, the use of such drugs might be suboptimal if the pharmacological target is the conducting airways, as most of a slowly dissolving drug will be removed through nonabsorptive mucociliary clearance from the central regions of the lungs. In later stage development, the effect on solubility/dissolution will need to be considered when bridging changes in formulation or device during manufacturing scale-up or when making postapproval changes.

When developing lead drug candidates are developed, potential technical and clinical challenges can be inferred from iBCS designation and used to develop product development risk mitigation strategies. In this way, inhalation scientists can use the iBCS in the way many oral product development scientists use the original BCS for drugs delivered to the gastrointestinal tract (giBCS); *i.e.* as a guide when selecting excipients or salt forms, identifying suitable manufacturing technologies and developing discriminatory *in vivo*-predictive dissolution methodologies to mitigate development risks.

The iBCS may also be applicable in later stage development programs, for example, to bridge changes in solid-form, formulation, or device, or for manufacturing scale-up or postapproval changes. While the iBCS class designation of a drug provides a scientific basis for streamlining product development of novel drugs, the iBCS was not developed to address the challenge of bioequivalence between the two ligands of the OIDPs. However, if a link between the iBCS class and bioequivalence requirements can be established, it may, with additional testing to establish regional deposition and device similarity (see sections 3.1 and section 5), facilitate generic OIDPs by eliminating the need for costly clinical end point bioequivalence (CEBE) studies.

To fully leverage the iBCS, it is important to understand its limitations and the practical gaps that hinder broader

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Mol. Pharmaceutics 2025, 22, 1740−1751

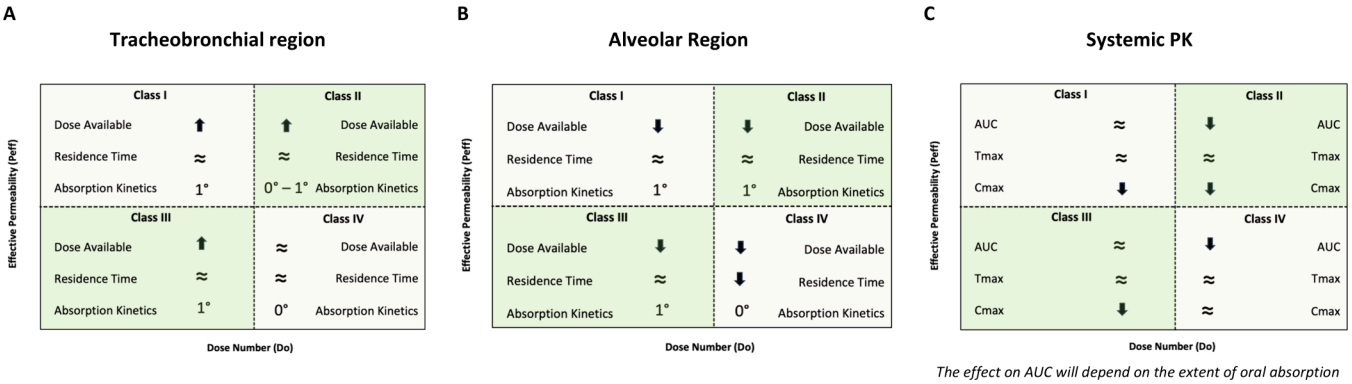

Figure 2. Impact of an Increase in Central to Peripheral Deposition Ratio. The effect of an increase in central to peripheral deposition ratio for inhaled products in each iBCS Class on (A) drug dose and residence time in the tracheobronchial regions of the lungs, (B) drug dose and residence time in the alveolar regions of the lungs, and (C) the rate and extent of systemic exposure. The dose available refers to the bioavailable dose, *i.e.* drug, that is available for absorption from the lung lumen in the region of interest (assuming an absence of metabolism). The residence time is the time it takes for the available dose to be absorbed, which can be described by mean absorption time within the lungs. The absorption kinetics are described as first order (1°) for sink conditions and zero order (0°) for nonsink conditions. The P_{eff} dividing line is 1×10^{-6} cm/s, and the Do dividing line is 1. Key: ≈ little or no change, ↓ a biorelevant reduction, ↑ a biorelevant increase, 1°: first-order absorption kinetics, 0°: zero-order absorption kinetics.

implementation. These gaps arise from the lack of predictive and standardized methods for characterizing inhaled products. Specifically, *in vivo* predictive methods must be developed for determining the lung dose, characterizing the dissolution of the formulated drug product, and measuring the pulmonary permeability of the drug, while accounting for tissue interactions.

Even without harmonized methods, the iBCS allows drug product developers to appraise the sensitivity of the rate and extent of inhaled drug absorption to formulation and device factors based on dose (potency) and molecular properties. For example, the iBCS describes a Class I drug as a molecule that would have complete dissolution in the lung and rapid absorptive clearance, implying that a drug in this class may lack sensitivity to formulation characteristics affecting dissolution. In contrast, the rate and extent of pulmonary absorption for a Class II molecule will depend on the dissolution rate as well as regional lung deposition. Absorption of a Class III molecule will be limited by permeability, and therefore the impact of excipients and other factors that can affect permeability need to be understood. Based on the current evaluation of marketed OIDPs, only high dose antibiotics would be classified as Class IV drugs. Although Class IV drugs are the most challenging inhaled drug candidates, marketed products with molecules in this category exist and more are currently in development.

The next section expands on the sensitivity of lung and systemic PK (product performance) to regional deposition and dissolution rate, illustrating clearly the implications of the iBCS class for how local and systemic exposure will change in response to these product attributes.

3. IMPLICATIONS OF IBCS CLASS FOR OIDP PERFORMANCE

Locally acting orally inhaled drug products are intended to achieve pronounced pulmonary therapeutic effects while minimizing systemic side effects, *i.e.* regional lung targeting with distinct lung selectivity. A long pulmonary residence time, due to either slow dissolution or low permeability, favors lung targeting[5] indicating that besides the pharmacological properties of an API (*e.g.* receptor binding affinity/receptor selectivity), properties affecting the lung residence time (*e.g.* slow dissolution rate, low permeability, high tissue binding, lysozyme trapping, slow dissociation from receptor sites) might be key API/formulation attributes. As described above, applying the iBCS classification system to inhalation drug development might, therefore, facilitate and rationalize development strategies, as they relate to selecting APIs with favorable physicochemical properties. As an example, the predicted fast dissolution and absorption of Class I drugs from central and peripheral areas of the lungs[2] suggests that, in contrast to Class II–IV drugs, iBCS Class I drugs are unlikely to show high lung selectivity unless they have specific interactions prolonging engagement with their lung target. Otherwise, their use may be limited to "hit and run" drug therapies or APIs used as rescue medications. On the other hand, Class I drugs might benefit from formulation approaches that prolong pulmonary residence, *e.g.* through encapsulation into liposomes, nano/micro particulates or other formulation approaches.[4]

While lung residence times of iBCS Class II–IV drugs are longer, lung retention will differ significantly for the alveolar and more central regions of the lungs. The alveolar region has anatomical and physiological features (a larger area, thinner epithelial barrier, and higher blood-flow compared to the central region) that favor fast absorption. The rapid absorption of iBCS Class II drugs from the alveolar region also prevents drug concentration from building up in the alveolar lining fluid meaning that dissolution of iBCS Class II drugs is likely to occur under sink conditions and will be faster compared to more central regions of the lungs where dissolution occurs under nonsink conditions. As an example, population pharmacokinetic analysis of fluticasone propionate dry powder inhaler data revealed absorption half-lives of about 15 min for the peripheral and 6 h for the more central portions of the lungs,[6] demonstrating the challenge of achieving pulmonary retention and targeting in alveolar regions of the lungs over an extended duration.

In the tracheo-bronchial region of the lungs the mucociliary escalator provides an efficient clearance mechanism, meaning that Class II and IV drug particles dissolving slowly under nonsink conditions will be removed from the central airways, resulting in incomplete bioavailability in this region and systemically if the drug is not orally absorbed.[7,8] This is especially true when dissolution is much slower than the

https://doi.org/10.1021/acs.molpharmaceut.4c01534
Mol. Pharmaceutics 2025, 22, 1740–1751

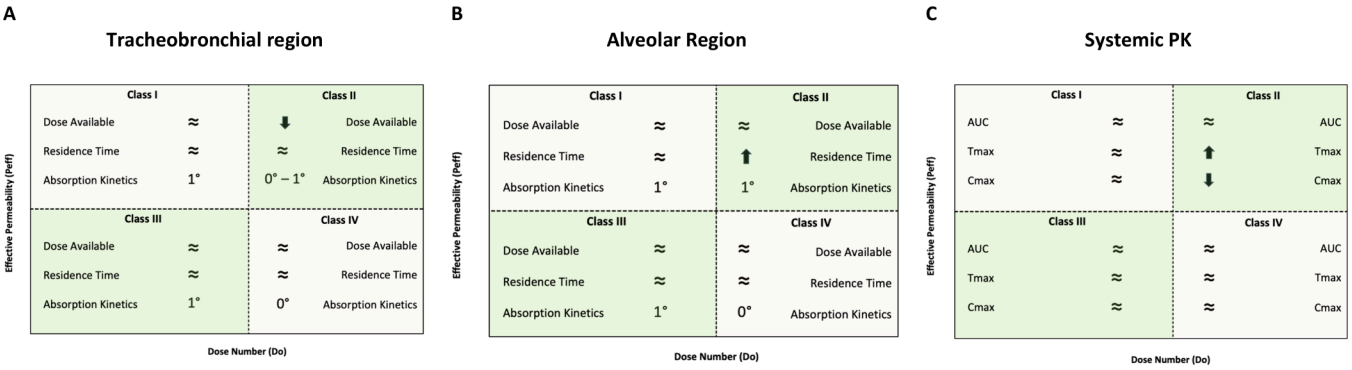

Figure 3. Impact of a Decrease in Dissolution Rate. Effect of a decrease in dissolution rate for inhaled products in each iBCS Class on (A) drug dose and residence time in the tracheobronchial region of the lungs, (B) drug dose and residence time in alveolar region of the lungs, and (C) the rate and extent of systemic exposure. The dose available refers to the bioavailable dose, *i.e.* drug that is available for absorption from the lung lumen in the region of interest (assuming an absence of metabolism). The residence time is the time it takes for the available dose to be absorbed, which can be described by mean absorption time within the lungs. The P_{eff} dividing line is 1×10^{-6} cm/s and the Do dividing line is 1. Key: ≈ little or no change, ↓ a biorelevant reduction, ↑ a biorelevant increase, 1°: first-order absorption kinetics, 0°: zero-order absorption kinetics.

mucociliary clearance rate, which is generally the case for Class IV drugs, making them unsuitable for targeting the central regions of the lungs. In the alveolar region, dissolution of iBCS Class IV drugs is likely to occur under zero-order kinetics for compounds for which even alveolar structures limit absorption. Clearance through the phagocytic activity of macrophages is likely to occur under these conditions,[9] although little is known about the efficiency of this clearance mechanism for iBCS Class IV drugs.

Beyond the API iBCS class, pulmonary pharmacokinetics depend on formulation-dependent critical performance attributes, such as regional lung deposition and factors affecting the dissolution rate, *e.g.* accessible particle surface area. The relevance and criticality of these product performance attributes for affecting the pulmonary and systemic exposure for different iBCS classes are considered individually in sections 3.1 and 3.2 below, *i.e.* assuming factors relevant for the dissolution rate will not affect regional deposition and vice versa. It is appreciated that, in reality, changes in regional deposition and dissolution are often interrelated; *i.e.* changes in aerodynamic particle size (MMAD) affecting regional deposition often occur concomitantly with changes in volumetric particle size (VMD) or other particle properties that affect dissolution. The effects deposition and dissolution on lung exposure and pharmacokinetics in sections 3.1 and 3.2 are largely based on the first-principle analysis performed in iBCS paper 2,[2] which was supported by the placement of inhaled drugs on the iBCS grid in iBCS paper 3.[3] Supportive experimental data have been referenced where available and appropriate and are further considered in section 3.3.

3.1. Effect of Regional Deposition on Pharmacokinetics. Increase in the central to peripheral deposition ratio (C/P) is a shift of drug deposition from the alveolar to the tracheabronchial regions of the lungs. This could occur due to changes in inhalation flow and/or aerodynamic particle size attributes. The effect of increasing C/P on lung exposure of iBCS Class I–IV drugs is presented in Figure 2, which shows the predicted impact on (i) the amount of drug available and pulmonary retention in central and peripheral areas of the lungs, and (ii) the rate and extent of systemic exposure (T_{max}, C_{max}, AUC).

In the alveolar region, dissolution and permeation processes for Class I–III drugs are described by first-order relationships, and an increase in the C/P ratio is not predicted to affect the alveolar residence times for these drug classes. In the central lung region, the extent of the increase in the dose available upon an increase in the C/P ratio will differ across iBCS Class I–IV drugs. For an iBCS Class II drug, the increase in the centrally deposited drug will only slightly increase the drug residence time due to mucociliary clearance of particles that are slowly dissolving under nonsink conditions. For Class IV drugs, a zero-order dissolution rate that is slower than the mucociliary clearance rate is likely, in which case an increased C/P ratio would translate into only a small, pharmacologically irrelevant, increase in the pulmonary residence time.[5]

The area under the plasma concentration time profile (AUC) will not be affected by increasing the C/P ratio as there is a direct relationship between drug loss in the alveolar region and an increase in available drug in the central lung region for Class I and III drugs. As iBCS Class II and IV drugs are subject to mucociliary clearance, increasing the C/P deposition ratio is not predicted to result in a linear increase in the centrally available dose as some of the increase in centrally deposited dose is expected to be removed by the mucociliary clearance (assuming negligible oral absorption or concomitant oral administration of charcoal). This is even more dramatic for Class IV drugs, for which the increase in the centrally deposited dose will not translate into a pharmacologically relevant increase in the regionally available dose, as the fraction of solid drug able to escape the mucociliary clearance will be close to zero because of very slow zero-order dissolution kinetics resulting from low solubility and low permeability.

An increase in the C/P ratio affects the C_{max} values for Class I–III drugs. A reduced C_{max} will be observed for Class I and III drugs because the amount of drug available to be absorbed quickly from the alveolar region is reduced. AUC values will not be affected for these iBCS classes, as the total amount of drug able to enter the systemic circulation has not changed. This is different for Class II and IV drugs; both impacted by solubility/dissolution, meaning that an increase in the C/P will result in a decrease in the C_{max}, and to a lesser degree a reduction in AUC (if the drug is not orally absorbed), because more drug will be removed from the central regions through mucociliary clearance and swallowed.[10]

3.2. Effect of Dissolution Rate on Pharmacokinetics. The effect of an increase in the dissolution rate on pulmonary and systemic PK is shown in Figure 3. This could occur due to

https://doi.org/10.1021/acs.molpharmaceut.4c01534
Mol. Pharmaceutics 2025, 22, 1740–1751

changes to volumetric mean particle size, formulation composition, or physical chemistry, *e.g.* polymorphic form. Factors affecting dissolution rate are predicted to have little effect on the fate of drugs with low dose number (Class I and III) in either the alveolar and central regions of the lungs or on the systemic pharmacokinetics as their dissolution occurs almost instantly.

For an iBCS Class II drug, residence time increases with a decreased dissolution rate in the alveolar regions of the lungs and to a lesser degree in the central regions of the lung due to mucociliary clearance. Formulation factors modulating dissolution (*e.g.* use of suitable excipients, or optimized particle sizes) might be used to enhance pulmonary selectivity, with maximum pulmonary selectivity being observed in the central regions of the lung if particle dissolution and mucociliary clearance rates are comparable.[5] A reduction in dissolution rate also affects systemic plasma concentration profiles by reducing C_{max} and, to a lesser degree, AUC.[7,8]

For a Class IV drug, dissolution and permeability-limited absorption in the alveolar and central regions of the lung are described by zero-order processes. Pulmonary targeting under these conditions will be pronounced in the alveolar region. However, the long residence time might result in accumulation of undissolved drug during therapy, resulting potentially in toxicological consequences.[11] Due to the slow dissolution of Class IV drugs, mucociliary clearance will efficiently remove drug particles from central regions and any contributing factor, *e.g.* increase in VMD, will further reduce the already negligible fraction of centrally available drug. Hence, the reduction in the dissolution rate for a Class IV drug will result in a drop in AUC with no effect on the C_{max}.

3.3. Evidence for the Effect of Regional Deposition and Dissolution on Pharmacokinetics. Several studies have demonstrated the effects of the dissolution rate and regional deposition on the pharmacokinetics of inhaled drugs.

The effect of dissolution rate on the pulmonary targeting of budesonide has been evaluated in rats.[12] Here, the dissolution rate was modulated through surface coating of the API particles, and more pronounced targeting was observed for the more slowly dissolving coated particles. The degree of pulmonary targeting for a range of inhaled corticosteroids has also been assessed, with pulmonary targeting increasing with increasing log *P*, which is associated with a slower dissolution rate.[13]

The effects of lung deposition changes induced by methacholine administration have been evaluated for two inhaled corticosteroids, budesonide and fluticasone propionate.[14] The authors observed a decrease in cumulative absorption (AUC0-inf) for the slowly dissolving drug fluticasone propionate, which was attributed to more budesonide and fluticasone furoate depositing in the more central regions of the lung upon methacholine challenge and the slower-dissolving fluticasone being removed from this section of the lung through mucociliary clearance, while the faster-dissolving budesonide was better able to evade particulate removal by the mucociliary clearance.

A more recent study evaluated the combined effects of changes in dissolution rate and particle size distribution of inhaled fluticasone propionate.[6,10] Dry powder formulations were prepared that differed in the dissolution rate and aerodynamic particle size deposition. Results of a population pharmacokinetic analysis suggested a more central distribution for larger particles, with more peripheral deposition resulting in a larger C_{max}. In addition, a strong correlation was found between dissolution rate differences and differences in the central and peripheral absorption rate. The difference in absorption rate were less pronounced for the more central regions of the lungs consistent with the close-to-zero-order dissolution kinetics in this region of the lung.[6]

4. CURRENT LIMITATIONS TO APPLYING THE IBCS

4.1. Methods for Measuring Lung Dose. The dose number is one of the three parameters that determine the iBCS class of an inhaled molecule. The dose number is derived from the total dose depositing in the lungs and is used to classify products for the iBCS. In contrast, regional distribution of the lung dose determines the fate of deposited drug particles and product performance (as discussed in section 3.1). Hence, the total lung dose and the regional distribution of the dose are both important to inhaled drug product development. There are many approaches to estimate or measure the total lung dose and the regional lung distribution of inhaled aerosols. These range from *in vivo* imaging studies using radiolabeled drug products, to *in silico* modeling based on *in vitro* testing, to *in vitro* testing alone.

It might be argued that *in vivo* deposition measurements are the "gold standard" for lung dose and regional lung distribution determinations. However, imaging techniques have limitations. Estimates of total lung dose are good, as imaging of lungs as an organ is reasonably reliable. However, regional distribution measurements suffer from the need to transform spatial distributions, as measured by planar (2-dimensional) imaging techniques, into anatomically meaningful regional distributions.

Most of the *in vivo* data available have been generated using planar scintigraphy that provides total lung dose and regional deposition using 2D regions of interest (*e.g.* central, peripheral, and intermediate).[15] These regions inevitably contain mixed airway generations, due to imaging overlay, making it difficult to correlate them with the anatomical distribution of the deposited drug. Although penetration index measurements (central to peripheral ratios) have been related to 24-h retention measurements (nonciliated airway retention) for insoluble aerosols, the relationships are confounded by the use of different definitions of regions of interest and large intersubject variability.[16] 3D single photon emission computed tomography (SPECT)[17] has also been used to assess regional deposition. Three dimensional shells are used instead of planar regions; however, the difficulties of relating spatial measurements to anatomical distributions still confound the usefulness of these techniques.

Additionally, all imaging techniques require the use of radiolabeled aerosols (generally labeled with technetium 99m, a gamma-emitting radionucleotide with a half-life of ~6 h) and are costly, time-consuming, and technically challenging in terms of aerosol labeling (except for droplet aerosols generated from aqueous solutions), and carry the risks associated with human exposure to radiation.

In vitro testing offers a faster, simpler, and cheaper approach. *In vitro* testing can be roughly grouped into three classes:

a. testing to determine delivered dose and the size distribution of particles or droplets followed by input of the resultant data to an *in silico* model of regional deposition (typically a one-dimension path model, or CFD)

b. testing employing a physical model of the oropharynx to filter the material deposited in this region and impactor measurement of the dose delivered ex-throat and size distribution of particles or droplets followed by input of

https://doi.org/10.1021/acs.molpharmaceut.4c01534
Mol. Pharmaceutics 2025, 22, 1740−1751

the resultant data to an *in silico* model of regional deposition

c. testing alone, employing either a physical model of the oropharynx and a number of airway generations or an apparatus that performs serial filtration of the delivered dose that mimics regional deposition in the lungs[18]

These approaches differ in experimental complexity, and each has associated limitations. For example, where the test product does not generate particles or droplets with homogeneous drug content the size fractions within the dose must be collected for drug-specific analysis and nonspecific techniques such as laser diffraction cannot be used.[19] Particle size measurement employing impactors or impingers have traditionally used a constant and specific air flow rate to enable calculation of the aerodynamic size distribution.[20] Consequently, the flow rate and volume of "inhaled" air used for aerosolization and/or dose delivery may not reflect patient breathing patterns and lung deposition outcomes. Use of a realistic patient inhalation profile is becoming more common but requires more complex apparatus with supplementary flow control and a mixing or holding chamber that may introduce additional errors such as particle losses or droplet evaporation.[21] Where physical models are used to represent human anatomical structures, these are typically rigid but can employ realistic mucus-like surface coating and versions of varying sizes can be used to represent patient variations within a population.[22]

In silico models used in conjunction with *in vitro* methods to predict regional lung deposition of aerosols fall into two main classes, one-dimensional (1D) whole lung models and three-dimensional (3D) computational fluid particle dynamics models. The 1D models are typically easier to use and require minimal computer resources but factor in fewer of the many complexities of airway geometry, dose delivery and inhalation conditions. Nonetheless, they have been shown to be capable of providing good predictions of total lung dose in comparison to *in vivo* experimental data.[23] The 3D models have been developed to accommodate more detail, dynamic moving airway geometries, and complex dose delivery and inhalation conditions but require considerably more computation and still need long computational times (often many days).

Comparison of SPECT studies with *in silico* data, requires translation of data from the two techniques into a similar format with some associated error and sacrifice of detail.[24] As discussed above, the data generated by 3D SPECT contain information on regional spatial deposition. Data has been generated in a limited number of subjects and this may be unrepresentative of "average" patients as subject-to-subject variability is significant.[25,26] For this reason, efforts have been made to validate subject-specific *in silico* data (employing airway geometry obtained from X-ray and CT images) against SPECT data from the same individuals. Though results from validation approaches are promising,[25] the challenge of satisfactorily validating the wide range of *in vitro* and/or *in silico* techniques for estimating regional lung deposition remains.

Cheaper and easier implementation has resulted in considerable ingenuity in the evolution of both *in vitro* and *in silico* tools that have been applied to the development and optimization of inhalation aerosol drug products. However, the most significant gap in the use of these tools to estimate detailed lung and regional deposition remains validation against dependable, detailed, and appropriate *in vivo* experimental data.

4.2. Solubility and Dissolution. The solubility of the lung dose in the volume of fluid available in the lungs is represented by dose number, which determines when dissolution becomes a critical quality attribute.[3] Despite high potency and having doses in the microgram range, the low solubility of inhaled corticosteroids places them in iBCS Class II, enabling a relationship between dissolution rate and absorption kinetics to be observed.[8,27,28] There are few examples, apart from AZD5423,[7] for other drug classes where an impact of dissolution in the lungs on pharmacokinetics has been demonstrated.

Solubility determination is complicated by its dependence on the medium in which solubility is measured.[29] Simple aqueous media such as phosphate buffered saline and Gambles solution, a salt solution that is sometimes misleadingly referred to as "simulated lung fluid", may accurately determine the drug solubility in the aqueous phase of the epithelial lining fluid (ELF) but will significantly underestimate the total capacity of the ELF to solubilize lipophilic drugs. To simulate the solubilizing capacity of ELF, solubility has been measured at 37 °C in phospholipid-based solutions, lung surfactant replacement products diluted to physiological concentrations of phospholipid, and more complex synthetic ELF simulants.[29,30] To complicate matters further, there has been relatively little research into whether factors such as age, smoking, or respiratory disease influence the composition or properties, *e.g.* pH of ELF can affect drug solubility or particle dissolution.[31] For application of the iBCS, simple methods are required (analogous to the pH adjusted aqueous buffer solutions and standardized simulated intestinal fluids that support the giBCS), but these should be contextualized for the physiology of the lung lining fluid.

Dissolution is a critical product attribute for inhaled dosage forms containing drugs with a dose number >1 under iBCS. For products assigned to iBCS Class II or IV, dissolution testing can support pharmaceutical development by assessing the impact of particle size distribution and excipients, discerning the effects of pharmaceutical processing and storage conditions, and providing data to support product stability and expiry date assignment.[32] Although not developed initially for regulatory purposes, the iBCS identifies when dissolution is a critical quality attribute that should be controlled and included in a product quality profile, which carries the implication that generic versions of such products should demonstrate similarity in dissolution and are being added into the guidance of regulatory agencies, *e.g.* United States Food and Drug Administration (US FDA) *Product-Specific Guidances for Generic Drug Development*.

There has been a profusion of dissolution methods developed and applied to inhalation aerosols in recent years, and these have been extensively reviewed.[29,33−36] Methods for preparing samples, collecting aerosols, and measuring their dissolution profiles are based on a mixture of readily available labware, existing pharmacopeial apparatuses, and bespoke apparatus. Dissolution methods can be broadly categorized as bulk fluid (*e.g.* USP apparatuses II, IV, and VII) or membrane techniques (*e.g.* Transwells, Franz cells, Respicell). The former may not represent the fluid restriction in the lungs and may overestimate dissolution rates, whereas the latter may introduce restrictions related to drug transfer across the membrane and nonsink conditions. When included in physiologically based biopharmaceutics modeling, the dissolution profiles (% dissolved vs time) of inhaled medicines can be based on experimental data or calculated according to particle size (regressed into volumetric

https://doi.org/10.1021/acs.molpharmaceut.4c01534
Mol. Pharmaceutics 2025, 22, 1740−1751

Table 1. Summary of Gaps in Methodology and Understanding for Each Element Contributing to Product Classification Under the iBCS[a]

Gap	Lung dose	Solubility/Dissolution	Permeability
Excipients/formulation approaches	Can lung targeting formulation approaches be developed (evaluated by difference between intravenous and inhalation delivery using a marker of target engagement)?	To what extent do current, or possibly future, excipients or formulation approaches modify drug release?	Do current, or possibly future, excipients used in inhaled formulations modify permeability?
Test methods	Methods for measuring total lung dose (regional lung dose is important for PK, but not for classification). Development of methods should include:	Development of "accepted" methods for determining aerosol dosage form dissolution:	Development of "gold standard" models for determining lung permeability is required. Considerations include:
	● Assay the amount of drug that is collected beyond the physiological throat when delivered by the OIPD.	● What medium should be used to measure solubility? Is equilibrium solubility for the drug substance determined at 37 °C in a "simple" medium, such as phosphate buffered saline, sufficient?	● How can variability in measurement between laboratories and methods be controlled? ● Which lung cell line(s) reflect *in vivo* tissue interaction?
	● The use of realistic breathing patterns.	● What aerosol fraction(s) should be tested and how should they be collected? Is use of a realistic throat to collect the entire dose for the dissolution sample (similar to the total lung dose method) suitable?	● Mass balance will need to be determined in the method(s).
	● Use of computational techniques, *e.g.* machine learning and simulation, to more efficiently and fully utilize experimental data.	● What apparatus and dissolution medium (composition/volume) should be used? ● Considerations for dissolution medium are similar to those for measurement of solubility. ● Using a USP dissolution apparatus may be advantageous, *e.g.* USP apparatus 5 or paddle over disk	● Studies should be conducted at 37 °C. ● Identify benchmarking compound for the high/low permeability threshold Methods for studying lung retention *in vitro* are an important need to enable drug screening and mechanistic studies of lung-retentive tissue interactions.
Research needs	● How do morphometric variables and morphometry-formulation interactions affect lung dose?	● More data to establish IVIVC for dissolution methods, including the use of silico modeling tools for PBPK	● New *in vitro* models to assess tissue retention (as above).
	● Development of *in silico* disease models.	● How can dissolution profiles be benchmarked to clinical relevance beyond PK?	● Do transporters affect lung permeability, and does this have clinical impact?
	● Development of new or improved noninvasive imaging techniques with higher resolution capabilities to measure lung dose and develop better IVIVC.	● What are the effects of age and disease on epithelial lining fluid; are there implications for drug solubility? ● Do we understand the risks of low solubility particles in the lungs, *e.g.* accumulation, irritation, adverse effects, low airway exposure to free drug?	● What are the effects of exercise, smoking, disease, metabolism on lung permeability? ● How does pulmonary permeability vary regionally and does this vary according to the route of transport by which the drug is absorbed?
Standardization and validation	Consensus is required to establish universal methods	Development of guidelines for discriminatory dissolution methods, including how data is analyzed and validated, and modeling approaches.	Assay methods are variable and complex. Simpler assays that are amenable to standardization are required, followed by validation by IVIVC.

[a]Collectively, this provides a rich research agenda that will require advances in biopharmaceutics modelling to combine and contextualize the *in silico*, *in vitro*, and *in vivo* data generated.

https://doi.org/10.1021/acs.molpharmaceut.4c01534
Mol. Pharmaceutics 2025, 22, 1740−1751

particle size distribution) based on dissolution theory. The latter provides an alternative to establishing "*in vivo*-like" dissolution methods by using models that predict dissolution profiles by considering the conditions at the epithelial surface (*e.g.* volume, solubility).[8] Experimentally determined dissolution provides a valuable complementary technique that can validate differences in particle size distribution measured by other techniques and test the impact of particle size and other formulation factors, *e.g.* lactose fines, on dissolution.[10]

The widespread differences in approaches to generating dissolution data for OIDPs make comparisons between studies difficult. Consolidation and standardization to make available a selection of robust, reproducible methods would help in this regard. The selection of an appropriate lung fluid simulant or dissolution method depends on the purpose of the measurement or assay. For example, if the testing is for critical product attributes as a means of controlling product quality, developers can develop and justify a methodology that works best for the products they are developing, as is the case for tablet dissolution. However, if the purpose is to conduct mechanistic investigations, then more biorelevant media and methods are required.

4.3. Permeability. As far as *in vitro* models are concerned, there is no generally accepted gold standard for measuring permeability in the pulmonary field that would compare to that of the intestinal Caco-2 cell line. The human respiratory mucosa varies greatly between conducting airways and the alveolar regions. The trachea and bronchi are lined by a ciliated pseudostratified columnar epithelium that is covered with mucus patches on top of liquid lining fluid, the depth of the latter is between 5 and 10 μm.[37] In the alveolar compartment, type 1 and type 2 alveolar epithelial cells are found.[38] The type 1 cells cover 90 to 95% of the alveolar surface.[39] The depth of the alveolar lining fluid is around 0.2 μm. The alveolar region also has luminal macrophages with a high phagocytic capacity.[40] Replicating this complex structure (in terms of epithelial barrier and clearance mechanisms) *in vitro* or *ex vivo* is challenging and over the last decades a variety of approaches have been tried, each with their advantages and limitations (for a review, see ref 41. For iBCS implementation, a simple and universal means of measuring P_{eff} for the purpose of biopharmaceutic classification is required. The importance of "tissue-retentive" mechanisms, regional variation in mucosal thickness and other transport barrier characteristics have yet to be fully determined, hence the pressing need for model development and validation.

The pulmonary absorption of free drug into the bronchial and pulmonary circulation may occur by either diffusion- or transporter-mediated processes. Although the relative contribution of each pathway is unknown,[42] there is little evidence to date for a clinically meaningful contribution of transporters to the absorption of marketed inhaled medicines.[43] Membrane transporters can be classified into passive transporters that do not require metabolic energy or active transporters that do. The latter is capable of transporting substrates against their concentration gradient. In theory, apically localized efflux transporters should extend the dwell time of drugs in the lungs, whereas uptake transporters should increase absorptive drug clearance or access to intracellular compartments such as lysosomes. However, reports of the net contribution of membrane transporters to pulmonary drug absorption are somewhat conflicting, which is likely the result of variable and poorly controlled experimental approaches, as well as species differences. Another issue when assessing the impact of transporters on membrane drug trafficking is the use of pharmacological inhibitors, which often lack selectivity and specificity.[44] The CRISPR-Cas9 technique allows for generation of cleaner models, and transporter knockout rats in combination with positron emission tomography scans offer a powerful new tool.[45] How well these new nonclinical data translate into clinically useful understanding remains to be seen.

Tissue binding, metabolism, and nonabsorptive clearance are important pulmonary drug disposition processes that are not accounted for in some permeability models and may influence permeability measurements in others. Drug tissue interactions that may influence lung residence times include mucus interactions, lysosomal trapping, and receptor binding. Lysosomal trapping has been reported for cationic drugs using precision-cut lung slices.[46] Mass spectrometry imaging has been used as a novel tool to measure regional localization and differential lung retention of inhaled salbutamol and salmeterol compared to fluticasone.[47] Emerging *in vitro* methods to investigate lung targeting include lung-on-a-chip approaches, which can be combined with the imaging techniques to quantify receptor targeting. *In vivo* approaches generally assess the difference between intravenous and inhalation delivery, using a suitable marker of target engagement.

Many *in vitro* and *ex vivo* systems are already available,[41] *e.g.* immobilized membranes, Caco-2 cells, organotypic cell lines, organotypic primary cell cultures, precision-cut lung slices, and isolated and perfused lungs. However, which models from what species are best suited to generate permeability data is currently under debate, and well-defined protocols are required that describe in detail how conduct absorption studies and control for laboratory-to-laboratory variation. The isolated perfused lung (IPL) method provides an opportunity to measure absorptive drug transport from the lungs as a whole and enables P_{eff} to be determined.[48,49] Despite its limitations in terms of throughput and technical complexity, the IPL is the current method of choice for measuring a P_{eff} value that incorporates "tissue-retentive" mechanisms.

4.4. Research and Development Requirements to Support the iBCS. The gaps in knowledge, research requirements, and the need to develop characterization and formulation development tools described in sections 4.1−4.3 are summarized in Table 1.

The iBCS has been developed for small molecules,[3] but the methods developed may also be useful or adapted for biopharmaceuticals and new modalities that are emerging as challenging inhaled drug candidates for OIDP developers. The influence of disease is relevant to all the iBCS classifiers: dose, solubility, and permeability.

Overall, the key enablers for applying the iBCS to the development of OIDP are

(i) Standardized, fit-for-purpose *in vitro* assays are required to measure solubility and permeability for iBCS classification of drugs. The criticality of dissolution rate for clinical performance will depend on iBCS drug class.

(ii) Permeability and solubility are molecular properties that can be established early in drug development, but there may initially be uncertainty about dose that is critical to enable dose number to be calculated. Dose can be estimated during early development, but will need to be established in clinical phases using reliable methods that predict and measure drug deposition to allow robust classification,

https://doi.org/10.1021/acs.molpharmaceut.4c01534
Mol. Pharmaceutics 2025, 22, 1740−1751

5. TOWARD BIOEQUIVALENCE

The value of an iBCS lies in its ability to aid inhaled drug development from drug discovery through postapproval. Although the iBCS by itself cannot be used to establish BE between two inhaled drug products, once discriminating analytical methods are in place, the class designation for an inhaled drug will provide an understanding of the critical product attributes, which, in turn, will inform product development and formulation strategies. Therefore, the potential for future implementation of a regulatory bioequivalence framework based on the iBCS does exist.

The key barriers to an iBCS-based BE framework mimicking that existing for oral drugs based on the giBCS are the same as those addressed here in the context of classifying drugs for the iBCS, *i.e.*, a lack of standardized methods to assess therapeutic dose, therapeutic dose deposition, solubility, dissolution, and permeability. The most critical of these gaps are likely to be found within the area of dose and dose deposition, as these properties are intimately linked with the design and performance of the inhaled drug-device combination and its patient handling. Hence, it is our belief that any iBCS-based BE framework must address this gap: how can we accurately assess dose and bioavailability? A possible solution is to request that the generic replacement drug product is essentially equivalent to the originator product in aspects of formulation, device, and dosing performance under clinically relevant conditions. This, in combination with class specific demands on dissolution testing and data on systemic PK could provide for a more generalizable approach to, *e.g.* CE-BE biowaivers for inhaled generics. To some extent, this thinking is also reflected in new draft product specific guidelines issued by the US FDA,[50] and by the draft EMA BE guideline for inhaled products.

Pharmacokinetic studies are generally a key component when determining the performance of inhaled products during bioequivalence assessments as described in recent EMA general guidance and FDA Product specific guidances. The scientific basis for this is provided in section 3. The analysis in Figure 2 suggests that in the absence of oral uptake of cleared and swallowed drug systemic PK is generally sensitive to regional variations in drug deposition within the lungs, independent of the iBCS classification. If the dissolution rate changes (Figure 3), the C_{max} values of iBCS Class II drugs and to a lesser degree AUC will be affected, while differences in particle properties generally modulating dissolution rate under sink conditions will not translate into clear differences in systemic markers of exposure (C_{max} and AUC) of iBCS Class IV drugs because of the presence of zero-order processes in central and peripheral regions of the lung. Due to rapid dissolution, the AUC and C_{max} values of iBCS Class I and III drugs are generally not observed, or predicted[23] to be affected by dissolution rate changes. Overall, this would suggest that pharmacokinetic bioequivalence studies, performed under charcoal-block if necessary, might be appropriate for the bioequivalence assessment of all iBCS drug classes (with the exception of identifying differences in dissolution rates for Class IV drugs). This provides a basis for PK studies to substitute for clinical end point studies, although such an approach would further emphasize the need for validated *in vitro/in silico* methodologies assessing regional lung deposition as powerful tools for derisking *in vivo* bioequivalence studies across all iBCS drug classes. A recent study validated the ability of CFD modeling of aerosol deposition to predict SPECT deposition data in six asthmatic patients[51] and the US FDA (GDUFA Science and Research Awards scheme U01FD007987) is supporting research into predictions of regional lung deposition produced by computational fluid dynamic (CFD) models to support the development of efficient BE approaches for OIDPs.

6. SUMMARY AND CONCLUSIONS

Inhaled drug product development is challenging and costly and requires a strong rationale to be viable and successful for the disease/target being considered. The first three papers in this series[1−3] identify the importance of dose number (based on lung dose, lung fluid volume and solubility) and permeability as key characteristics defining the utility or development strategy of a drug as an inhaled therapeutic. This paper emphasizes that the classification of an inhaled drug based on the iBCS provides us with an understanding of the critical product attributes of the drug product, and once harmonized methodologies are in place, application of the iBCS will be able to provide us with a science-based approach to facilitate drug product development, postapproval changes, and developments in OIDP regulation. For example, for OIDPs that are solubility and/or dissolution rate limited (*i.e.* iBCS Class II and IV), dissolution will be a critical drug product attribute. For these products, in addition to the control of delivered dose and the aerodynamic particle size distribution throughout the product shelf life, the dissolution of the drug product also needs to be monitored and controlled in order to achieve reproducible product performance.

The development of *in vitro* and *in silico* tools has evolved significantly in recent years with the specific intent of their application to the development and optimization of the OIDP. The priority for science and method advancement is new and improved tools to estimate total lung dose and regional lung deposition by validation against reliable and detailed *in vivo* experimental data. To address this deficiency imaging techniques such as PET and SPECT have been used but do not completely address the need. New methods should exploit the latest scientific and technical advances to model target patient populations to ensure the "real-world" relevance of total and regional dose estimates.[52]

Dissolution is increasingly accepted as a critical product attribute for inhaled dosage forms containing poorly soluble drugs (dose number >1 under iBCS). Comparisons between studies generating dissolution data for OIDPs are difficult because of the absence of a standard method. Consolidation of existing methods and where possible their standardization as robust and reproducible methods are the priority here to reduce the difficulty in comparing and interpretating available data. The aim should be to establish the simplest, most robust methodology for which biorelevance of dissolution data can be established, *e.g.* by using mechanistic *in silico* modeling to translate key drug and product properties into *in vivo*-predictive dissolution profiles.

The relative impact, both qualitative and quantitative, of membrane transporters, tissue binding, intracellular trapping, mucus and surfactant interactions, and macrophage phagocytosis in the lungs remain uncharacterized. Currently, these are captured through the use of the IPL to determine P_{eff}. The development of *in vitro* methods to study drug (and ideally formulation) interactions with these elements of lung biology is needed and may collectively lead to a better mechanistic understanding of lung absorption, including the extent to which conducting airways and alveolar absorption contribute to local disposition or systemic absorption.

https://doi.org/10.1021/acs.molpharmaceut.4c01534
Mol. Pharmaceutics 2025, 22, 1740−1751

In developing the iBCS, we have demonstrated that existing drug products fit the broad principles and classification framework. However, it should certainly not be concluded that all questions have been answered in addressing the delivery and disposition of drugs to and from the lungs. It is evident from our overarching observations that further research is critical to establish or adopt standardized methods from which relevant data can be generated to support the iBCS. There remain important unanswered questions relating to the identification and standardization of methods that will allow the iBCS to be applied as broadly as possible and ultimately linked to an IVIVC, that could support bioequivalence comparisons.

The challenges associated with OIDP development are numerous, and the development path is often complicated by switching of devices and/or formulations as development progresses. The iBCS framework allows for a common terminology and useful guideposts to guide developers across all stages of development. The questions and gaps in knowledge exposed during development of the iBCS (*i.e.* those we describe herein) provide a clear call to arms for more fundamental research and method standardization. If this heralds a concerted response by researchers to address these needs, then the iBCS provides a framework through which the OIDP drug development process can be "fine-tuned" based on the iBCS class designation.

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Funding

The development of an inhalation-based biopharmaceutics classification system (iBCS) was an initiative supported by the Product Quality Research Institute (PQRI).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This manuscript reflects the views of the authors and should not be construed to represent FDA or other organizations' views or policies.

ABBREVIATIONS

API	Active Pharmaceutical Ingredient
APSD	Aerodynamic Particle Size Distribution
AUC	Area under the Plasma Concentration Time Curve
BE	Bioequivalence
CEBE	Clinical End Point Bioequivalence
CFD	Computational Fluid Dynamics
C_{max}	Maximum Plasma Concentration
CMC	Chemistry, Manufacturing, and Control
C/P	Central to Peripheral Deposition Pattern
CT	Computed Tomography
Do	Dose Number
ELF	Epithelial Lining Fluid
EMA	European Medicines Agency
FDA	Food and Drug Administration
GDUFA	Generic Drug User Fee Act
giBCS	Gastrointestinal Biopharmaceutics Classification System
iBCS	Inhalation Biopharmaceutics Classification System
IPL	Isolated Perfused Lungs
MAT	Mean Absorption Time
MCC	Mucociliary Clearance
OIDP	Orally Inhaled Drug Product
P_{eff}	Effective Epithelial Permeability
PBBM	Physiologically Based Biopharmaceutics Modeling
PQRI	Product Quality Research Institute
PSG	Product Specific Guidance
SPECT	3D Single Photon Emission Computed Tomography
$T_{1/2}$	Half Life
T_{max}	Time to C_{max}
USP	United States Pharmacopeia
VMD	Volume Mean Diameter

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https://doi.org/10.1021/acs.molpharmaceut.4c01534
Mol. Pharmaceutics 2025, 22, 1740−1751