

iBCS: 1. Principles and Framework of an Inhalation-Based Biopharmaceutics Classification System

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ABSTRACT: For oral drugs, the formulator and discovery chemist have a tool available to them that can be used to navigate the risks associated with the selection and development of immediate release oral drugs and drug products. This tool is the biopharmaceutics classification system (giBCS). Unfortunately, no such classification system exists for inhaled drugs. The perspective outlined in this manuscript provides the foundational principles and framework for a classification system for inhaled drugs. The proposed classification system, an inhalation-based biopharmaceutics classification system (iBCS), is based on fundamental biopharmaceutics principles adapted to an inhalation route of administration framework. It is envisioned that a classification system for orally inhaled drugs will facilitate an understanding of the technical challenges associated with the development of new chemical entities and their associated new drug products (device and drug formulation combinations). Similar to the giBCS, the iBCS will be based on key attributes describing the drug substance (solubility and permeability) and the drug product (dose and dissolution). This manuscript provides the foundational aspects of an iBCS, including the proposed scientific principles and framework upon which such a system can be developed.

KEYWORDS: *biopharmaceutics classification system, inhaled drugs, iBCS, pulmonary drug delivery, PBPK, mechanistic modeling, critical product attributes*

1. INTRODUCTION

Development of a classification system for inhaled drugs based on drug substance physicochemical properties and drug product performance attributes would provide a qualitative assessment of the technical and clinical risks associated with the development of a new chemical entity or a new orally inhaled drug product. With the appropriate analytical methodologies in place to assess the critical physicochemical and performance attributes, an inhalation-based biopharmaceutics classification system (iBCS) for an inhaled drug might also provide insight into the possibility to achieve *in vitro*–*in vivo* correlations based on the specific drug iBCS classification. However, as with the oral immediate release biopharmaceutics classification system (giBCS), an iBCS is not intended to a priori determine bioequivalence (BE) but it will provide an understanding of the product development risks. The giBCS has been successfully developed and employed to achieve these goals and provide insight into product development technical and clinical risks based on drug classification.¹ Although the routes of administration are different, researchers have hypothesized that a similar classification system and approach could be established for orally inhaled drug products.²

As with the giBCS, it is proposed that an iBCS should be based on key attributes that govern the rate and extent of uptake of a medicine. Therefore, by analogy, these attributes would be specific to the drug substance (e.g., solubility and permeability) or to the drug product (e.g., dose and dissolution

rate). Due to the limited number of inhaled drugs, we propose that the class boundaries of a potential iBCS grid be delineated using model compounds with varying solubilities, permeabilities, and regional doses that span those of inhaled drugs. Using PBPK computational models, the physicochemical and product attribute will be used to derive functional output parameters, and the combined data set can then be used to set class boundaries. It is anticipated that these class boundaries will differ from those of the giBCS due to the physiological differences associated with the routes of administration. This will enable an evidence-based iBCS to be proposed, which will then be critiqued based on its ability to provide meaningful differentiation (classification) of existing orally inhaled drug products based on known technical and clinical challenges.

The research effort to develop an iBCS is supported by the Product Quality Research Institute (PQRI). PQRI (<https://pqri.org/>) is a nonprofit consortium of organizations that brings together members of the pharmaceutical industry, academia, and regulatory agencies to develop science-based

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approaches to regulation. The goal of the PQRI iBCS project is to generate a qualitative classification system that can be utilized by inhalation scientists as a “Rule of Thumb” to identify and manage CMC product development risks. This manuscript will propose the foundation (principles and framework) upon which an iBCS can be developed.

2. THE iBCS AND THE giBCS—COMPARISON AND CONTRAST

Biopharmaceutics is the relationship between the physical and chemical properties of the drug substance, the dosage form, and the rate and extent of drug delivery to the site of action. The giBCS provides a framework for classifying immediate-release (IR) solid oral dosage forms based on the *in vitro* dissolution characteristics of the drug product and factors that govern the rate and extent of drug absorption: dissolution rate, solubility, and intestinal permeability.¹ The giBCS states that if two drug products, containing the same drug, have the same concentration time profile at the intestinal membrane surface, then they will have the same rate and extent of absorption. In addition, this implies that if two products have the same *in vivo* dissolution profile under all luminal conditions, they will have the same rate and extent of drug absorption.

The giBCS classifies oral immediate release drugs into categories based on properties that contribute to the rate-determining steps controlling drug absorption. Using the principles of solubility of the highest dose and permeability, drug substances can be classified into one of four quadrants on the giBCS grid, reflecting the four giBCS classes.

- Class I – high solubility and high permeability
- Class II – poor solubility and high permeability
- Class III – high solubility and poor permeability
- Class IV – poor solubility and poor permeability

Currently, biowaivers can be granted for high solubility and high permeability (i.e., Class I) as well as high solubility and low permeability (i.e., Class III) drugs in oral IR solid dosage forms that exhibit similarly rapid or very rapid *in vitro* dissolution using recommended test methods for determining solubility, permeability, and *in vitro* dissolution.³ Obtaining a biowaiver provides the applicant with a waiver of *in vivo* BE studies, but it is not a waiver of BE. In order to achieve a biowaiver for a giBCS class III drug, the drug product test formulation composition must be qualitatively the same and quantitatively very similar to the reference product, and for a giBCS Class I drug, the drug product must not contain any excipients that will affect the rate or extent of absorption of the drug in order to achieve a biowaiver.

Since the giBCS was developed based on fundamental scientific principles that govern the rate and extent of uptake from a solid dosage form, these same principles should be applicable to the development of an iBCS as long as one accounts for the physiological factors that impact solubility, dose, dissolution, and absorption.² This should be the case even when the ideal product characteristics are different—which is the case for inhaled and oral immediate release drugs as shown in Table 1.

A comparison of BCS-based product characteristics for oral drugs and those proposed for inhaled drugs are provided in Table 2. Within the following section, the factors impacting dose, solubility, dissolution, and absorption (permeability) for inhaled drugs and oral drugs will be compared and contrasted

Table 1. Ideal Product Characteristics for Drugs Delivered by Oral vs Inhaled Routes of Administration

characteristic	oral drugs with systemic activity	inhaled drugs with local activity
target site of action	systemic	local
rate of systemic absorption	rapid	slow
rate of systemic clearance	slow	rapid
oral bioavailability	high	low

Table 2. Characteristics of Oral and Inhaled Drug Products Based on BCS Classifiers and Grids

BCS class	classifiers		product characteristics by route of delivery	
	solubility	permeability	oral route (giBCS)	inhaled route (iBCS)
I	high	high	complete dissolution	complete dissolution
			complete absorption	rapid absorptive clearance from the lung
II	low	high	incomplete dissolution	incomplete dissolution of the lung dose ^a
			complete absorption	dissolution dependent absorptive clearance
III	high	low	complete dissolution	complete dissolution of the lung dose
			incomplete absorption	permeability dependent absorptive clearance
IV	low	low	incomplete dissolution	incomplete dissolution of the lung dose ^a
			incomplete absorption	dissolution and/or permeability dependent absorptive clearance

^aAs for the GI tract, incomplete dissolution of the lung dose refers to the dissolution process being slower than the process of non-absorptive clearance of solid drug from the targeted site of absorption (here, the lung) resulting in incomplete absorption; i.e., the fraction dose absorbed from lung is <1 (see also eq 1).

to demonstrate how a BCS approach can be applied to the classification of inhaled medicines.

2.1. Factors Impacting Dose and Deposition. As noted in Table 1, most inhaled drug products are locally active and ideally are designed to have low to no systemic activity, whereas oral drug products are typically systemically active and are therefore designed to have high permeability and systemic bioavailability. Besides this important distinction, drug delivery differences are also manifested by the dose and the time-course for presentation of the dose by each route of administration. For oral dosage forms, the dose is defined as the amount of drug in the dosage form (i.e., label claim). Most inhaled drugs are drug–device combination products and require the use of an inhalation device to deliver the dose to the site of action. The lung dose for an inhaled drug product is defined as the amount of drug inhaled into the lungs, which is a fraction of the nominal dose. The lung dose is impacted by the interactions between the drug formulation and the device, and between the device and the patient. The emitted aerosol is characterized using *in vitro* aerosol performance test methods

that are specific and unique to inhaled drug products.^{4–6} The amount of drug leaving the mouthpiece of the device is defined as the emitted dose. Since a portion of the emitted dose can impact in the mouth or the back of the throat and be swallowed, the respirable dose must be further refined by characterizing the aerodynamic particle size distribution (APSD) of the delivered dose. The APSD of the inhaled aerosol can be described as a bimodal log-normal size distribution described in terms of three parameters: coarse fraction (CF, fraction of upper mode assumed to deposit in the mouth–throat) and mass median aerodynamic diameter (MMAD), and geometric standard deviation (GSD) of the lower mode (mass fraction of lower mode = 1 – CF).^{4,7}

For an inhaled drug product, once the drug leaves its “packaging”, the properties of the formulation, the delivery efficiency of the device, and the breathing maneuver of the patient all impact the lung dose and the dispersed particle size and distribution. The architectural differences of the airways between patients also impact the distribution of the lung dose from patient to patient.⁸ Therefore, it is the combination of the inhaled drug product and the patient that dictates the regional lung dose and deposition. Variation in both product attributes and patient interaction with the product will impact how much drug is deposited in the lung (the dose) and the distribution of the dose within the lung (regional dose).

Anatomically, the gut is divided into various regions (i.e., stomach, duodenum, jejunum, ileum, and large intestine) in which dissolution and absorption occur as the drug travels through the gastrointestinal tract. Similarly, the lungs can be divided into two regions: the conducting (or central) airways and the peripheral airways into which an inhaled drug is deposited simultaneously upon inhalation. The central airways (~2 m²) include the trachea and bronchi.^{9,10} These airways are ciliated and lined with mucus, and their role is to both “conduct” air to the peripheral regions of the lung and protect the airways by removal of insoluble and mucus bound materials by mucociliary clearance. The alveolar ductwork and alveoli which form the peripheral region of the lung are responsible for gas exchange. The alveoli are lined with a thin layer of surfactant (~0.2 μm) and have a much larger surface area (~100 m²) compared to the central airways.^{9,10} Deposition of the dose can be described by the central to peripheral deposition ratio (or C/P) which can be derived from gamma scintigraphy studies or modeled based on lung deposition computer models.^{11–13}

2.2. Factors Impacting Solubility and Dissolution.

Physiological differences between the GI tract and the lungs that impact solubility and dissolution rate include the pH and fluid composition and the volume available for dissolution of a drug *in vivo*. The pH throughout the lung is fairly constant at approximate pH 6.7 for healthy individuals, whereas the pH throughout the gut varies from pH 1.4 to 7.4.^{14,15} There is more fluid in the gut than within the location-specific viscous fluid layers that exist within the lung. In the gut, the amount of fluid is approximately 500 mL.¹⁶ Since the dissolution event for an IR oral dosage form is assumed to occur in the stomach, the giBCS assumes a volume of 250 mL of fluid available for dissolution of the orally administered IR dose. In contrast, the amount of epithelial lining fluid (ELF) in the lung available for dissolution of a pulmonary deposited dose is on the order of 10–70 mL. Although this “fluid” is fairly constant in terms of pH, the composition and volume of ELF is lung region and disease state dependent.¹⁷

The dissolution number, Dn, in the giBCS (eq 1) provides an estimate of whether there is enough time for the drug to dissolve based on solution volume and flow rate through the GI tract. Therefore, the dissolution number is dependent upon the transit time of the drug through the GI “tube”. For both oral and pulmonary drugs, if the dissolution is slow, absorptive and nonabsorptive clearance mechanisms will impact the amount of drug available for activity.

$$Dn = \frac{DC_s}{r_0} \cdot \frac{4\pi r_0^2}{\frac{4}{3}\pi r_0^3 \rho} \cdot t_{\text{res}} = \frac{t_{\text{res}}}{t_{\text{diss}}} \quad (1)$$

where Dn is the dissolution number, D is the diffusion coefficient, C_s is the drug solubility, r_0 is the initial radius, and ρ is the density of the particle, respectively; t_{res} is the residence time (which the giBCS defines as 4 h), and t_{diss} is the dissolution time.

Models for dissolution are typically based on the early work of Noyes–Whitney, Nernst–Brunner, and Fick,^{18–21} in which dissolution rate is proportional to particle size or surface area, the diffusion coefficient, and the concentration gradient, while inversely proportional to the diffusion layer thickness. The Nernst–Brunner equation, which is an adaptation of the Noyes–Whitney equation, is shown below.

$$\frac{dM}{dt} = \sum_{i=1}^n \frac{DS_i(t)}{h_i(t)} (C_s - C_t) \quad (2)$$

where M is the total amount of drug dissolved, D is the diffusion coefficient, S is the surface area, h is the diffusion layer thickness, C_s is the solubility of the drug, C_t is the concentration of the drug in solution at time, and t and i represent the various particle size fractions of the distribution.

The dissolution number used in the giBCS assumes that the volume of the particles is negligible when compared to the volume of the solution phase and incorporates the time course of volumetric flow in the intestine and accommodates the change in particle size over time.²²

In the lungs, given the limited volume of ELF and drug deposition onto a surface film instead into a bulk solution and the lack of plug flow as is used to describe the transit through the GI tract, the use of mathematical computer simulation models describing dissolution of polydisperse particles by Hintz and Johnson²³ can be combined with that of Nernst–Brunner to describe dissolution of particles in the lungs.

Dissolution rate can be impacted by formulation factors which include drug loading, particle size, solid form of the drug (e.g., crystalline or amorphous), ionic charge, and the type and amount of each excipient. Notably particle size, rugosity, and shape are the morphological features of inhaled aerosols that are responsible for the specific surface area of solid particles. As discussed, computational and experimental approaches are being developed to predict the impact of formulation on pulmonary absorption by modeling the dissolution process, e.g., predicting the dissolution of the particles using the Nernst–Brunner equation, using experimental dissolution data,²⁴ or modifying dissolution models used for oral absorption.²⁵ Although a review of specific dissolution methods for inhaled drugs is outside the scope of this manuscript, an upsurge of interest in experimental methods for studying the dissolution of inhaled medicines has led to a wide variety of methods being developed for this purpose.^{26–36} The interested reader is encouraged to review the referenced work

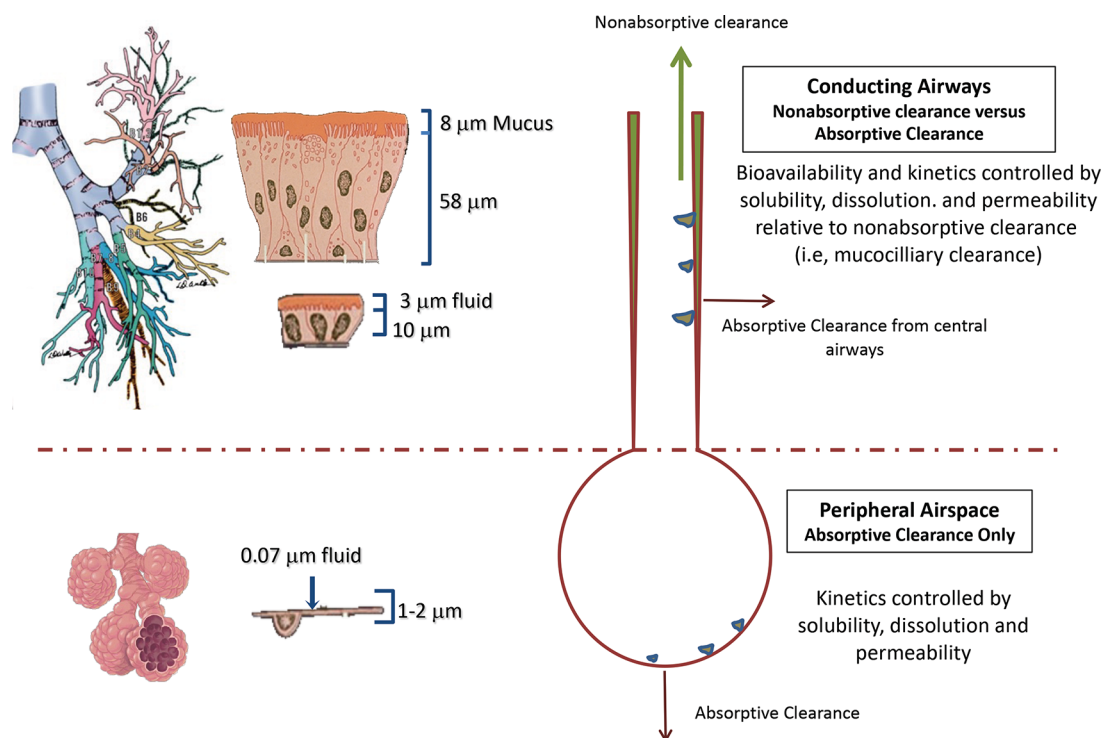


Figure 1. Schematic of clearance mechanisms from the lung as a function of deposition based on iBCS principles.

on this topic and note the wide variation in the methodologies being investigated. At this point in time, a harmonized pharmacopeial method to measure particle dissolution has not been identified, and dissolution testing is not commonly performed for commercial pulmonary drug products. Of course, in order to implement an iBCS, a dissolution method will need to be developed and validated.

2.3. Factors Impacting Absorption (Permeability).

The transit time of the oral dosage form through the gut is referred to as the GI transit time. The GI transit time can be impacted by food, disease state, and even the time of day a dose is taken. In healthy individuals, the total transit time is typically around 24–36 h.³⁷ The small intestinal transit time is estimated to be 3.2 ± 1.3 h.³⁸ For the giBCS, the transit time is defined as 4 h and is derived from a reasonable approximation of volumes and flow rates through the regions of the gut over which drug absorption occurs (e.g., the duodenum, jejunum, and ileum).³⁹

The giBCS describes the absorption number, An , as the ratio of the mean drug residence time, t_{res} (4 h) to the mean drug absorption time, t_{abs} (eq 3).

$$An = \frac{P_{eff}}{R} \cdot t_{res} = \frac{t_{res}}{t_{abs}} \quad (3)$$

where P_{eff} is the effective permeability and R is the approximate radius of the small intestines (1 cm). Similar to the gut, absorption can occur throughout the various regions of the lung. The clearance mechanisms from both the gut and the lungs can be defined as absorptive and nonabsorptive.⁴⁰ For the gut, absorptive clearance occurs by transport through the gut wall (absorption), whereas nonabsorptive clearance can be attributed to enzymatic degradation and clearance of undissolved drug in the feces (i.e., the gut is a flow-through tube).

For the lungs, defining a mean drug residence time using a plug flow is not appropriate, since the lung is more like a bucket into which the drug lands rather than a tube through which the drug transits. Even though there is not a “plug flow” within the lung that can be used to estimate a residence time, there are absorptive and nonabsorptive clearance mechanisms that contribute to the disposition of the lung dose. The nature of nonabsorptive clearance mechanisms from the lung depends on the dissolution rate of the deposited particle and the site of deposition.⁴⁰ When inhaled particles deposit in the ciliated central regions of the lungs, the dominant nonabsorptive clearance mechanism is mucociliary clearance (MCC), whereas insoluble particles reaching the alveoli are cleared by macrophages.^{41,42} Nonabsorptive mucociliary clearance transports particulates from the central airways into the oral cavity where they can be swallowed. Thus, nonabsorptive clearance from the lungs mainly affects slowly dissolving drug particles deposited in the conducting airways with dissolution rates that are slower than mucociliary clearance. Absorptive clearance from the lungs occurs by permeation into and across the lung epithelium and therefore by transport mechanisms that are similar to those for orally administered drugs across the intestinal epithelium. The latter process is thus dependent on molecular properties such as permeability, lipid partitioning, and affinity to active and passive transporters.

As mentioned previously, another key difference between the oral route of administration and the inhaled route of administration is that the lung dose is deposited in the central and peripheral regions of the lungs simultaneously with the breathing maneuver, whereas the orally administered dose is deposited in the stomach first and traverses through the GI tract over time. Therefore, dissolution and absorption processes are occurring simultaneously throughout the lung as opposed to the regional, plug flow-dependent dissolution and absorption associated with GI transit (see Figure 1). Since

the residence time in the lung is dependent upon multiple drug-specific factors as described above, as well as where the drug lands within the lung (regional deposition), it is much more difficult to express the residence time of inhaled drugs by a simple equation as has been done for oral drugs.

In vitro models to assess lung permeability are still being developed. In contrast to the general acceptance of Caco-2 cell cultures for providing estimates of permeability for the giBCS, a model to measure lung permeability of a drug has yet to be defined to support an iBCS.^{43,44} The lack of a standardized *in vitro* model is another gap which will need to be addressed before an iBCS can be fully defined and implemented.

3. IBCS BASIC PRINCIPLES AND FRAMEWORK

Taking into consideration differences in physiology and the route of administration as discussed in the previous section, the basic giBCS principles and framework can now be extrapolated to that of an iBCS.

Basic Principles of an iBCS. 1. For any given inhaled drug, the regional dose, solubility, dissolution rate, and permeability will dictate the local concentration time profiles within the lung lumen.

2. When two inhaled drug products containing the drug in the same solid state and with the same excipients can produce identical regional dose deposition patterns and dissolution rates, they will have the same local concentrations within the lumen and thus the same rate and extent of drug absorption from the airway lumen into the lung tissue.

The preceding statements form the framework for the conceptual development of an iBCS grid and are akin to those of the giBCS. For a pulmonary drug product, the dose and deposition are driven by the formulation, the device, the breathing maneuver, and the patient's airway geometry. Dissolution is driven by the formulation composition and the impact of the manufacturing process on drug properties such as particle size, morphology, and solid state. Permeability and absorption are driven by molecular properties and the drug concentration gradient. To develop an iBCS, the disposition of the regional dose within the lung will be modeled based on the physicochemical properties of the drug and performance attributes of the product using a PBPK model.

4. IBCS DEFINITIONS

The approach used to identify the iBCS grid and considerations for the classification boundaries must be based on practical considerations as defined below.

Pulmonary Deposition Regions. For the purpose of identifying the classification boundaries, two pulmonary deposition regions (central and peripheral) and whole lung will be considered. The central region (Bb) consisting of the large and small bronchial airways is defined as generations 0–16, whereas the peripheral respiratory region (Al) consisting of the alveoli and alveolar ducts is defined as generations 17–23.⁴⁶

iBCS Solubility. This is defined as the solubility of the drug in the ELF at the site of deposition. For the iBCS sensitivity studies, in order to explore perturbations due to changes in solubility, the medium need not be specified, since solubility will be used as an input parameter in the PBPK model.

iBCS Dissolution. This is defined as the rate of drug release/solubilization within the ELF. The volume available for dissolution used in the modeling will be estimated based on

regional surface area and ELF depth and will conservatively be set at a total volume of ~10 mL in the lung composed of 2 mL the central region and 8 mL in the peripheral region.² The dissolution rate is determined using a modified Hintz and Johnson dissolution model that takes into consideration dissolution on a wetted surface and assumes a diffusion layer thickness (h) of ten times the ELF depth for smaller particle sizes.^{23,25} The equation from Hintz and Johnson is provided below and expresses dissolution rate in terms of the initial solid dose (M_i) and particle radius (r_o) for a series of particle fractions i :

$$-\frac{dM_i}{dt} = \frac{3DM_o^{1/3}M_i^{2/3}}{\rho hr_o} \left(C_s - \frac{M_{d_t}}{V} \right) \quad (4)$$

where D is the drug diffusivity, M_o represents the initial mass of drug of a given size, radius (r_o), and density (ρ), h is the diffusion layer thickness, M_{d_t} is the total mass of dissolved drug for all particle fractions, V is volume, and t is time.

The dissolution rate is determined using the initial geometric particle size distribution for the inhaled drug product as defined by an apparent volume median diameter (VMD_{app}) and an apparent geometric standard deviation (GSD_{app}). For the iBCS grid boundary sensitivity analyzes, the particle size distribution will be specified as input parameters to the model.

iBCS Dose. This is defined as the total amount of drug deposited into the central and peripheral regions of the lung. The pulmonary dose number is defined in the same manner as the giBCS:

$$D_o = \frac{(M_i/V_i)}{C_{s_i}} \quad (5)$$

where D_o is the dose number for region i , M_i/V_i is the regional concentration of the initial dose in mass per volume of ELF, and C_{s_i} is the regional solubility.

Lung and regional dose values used in the PBPK model will be specified and therefore are independent of the device; e.g., the dose is “placed” in the regional compartment of interest in order to define the boundary between “high” and “low” solubility and dose number. Various deposition ratios (C/P ratios) will be explored to model disposition of the lung dose. The dose available for absorption is the amount of drug deposited in the lung minus the amount of drug cleared by nonabsorptive clearance mechanisms (i.e., MCC).

iBCS Permeability, P_{eff} . Permeability is defined as the effective epithelial permeability (P_{eff}) and is the rate at which the drug permeates into and through the respiratory absorption barriers and therefore represents the rate of disappearance (or absorptive clearance) of the drug from the lung lumen. The flux of free drug is determined by Fick's first law and assumes that transport is based on effective permeability and the concentration gradient across the membrane and ignores tissue interaction, active transport, and receptor binding.

$$J_i = P_{eff} \times \Delta C_i \quad (6)$$

where J_i is the flux of drug from the lumen into the epithelium in region i , P_{eff} is the regional effective epithelial permeability, and ΔC_i is the concentration across the barrier. For sink

conditions, the value of ΔC_i is the concentration at the epithelial surface. The epithelium is treated as a two-dimensional barrier.

Model P_{eff} values will be used as input parameters for the PBPK model sensitivity studies to determine the iBCS grid boundaries. As with the approach used to identify the high/low giBCS permeability class boundary, the model compound properties (input parameters) used to determine the iBCS permeability boundary exclude lysosomal trapping, receptor site binding, and general tissue interactions and the effect of charge.⁴⁵

5. DEFINING THE GRID BOUNDARIES

The approach used to map the critical attributes or classifiers onto an iBCS grid and thus define the grid boundaries will involve the use of computer-based multiscale mechanistic models. The sensitivity of the rate (half-life in the lumen) and extent (regional bioavailability) of uptake into lung tissue are based on variation of dose, solubility, and permeability (P_{eff}). The values that will be used for dose, solubility, and P_{eff} will be selected to include those of existing inhaled drug products. Given the variation in lung physiology between conducting airways and respiratory region, sensitivity modeling studies will be conducted for each of these regions as well as for the whole lung using various C/P ratios for deposition of the lung dose.

Functional output parameters will include descriptors of the rate and extent of drug availability within the lung. The rate of uptake will be characterized by the drug half-life in the luminal space of the lung ($t_{1/2, \text{lung}}$). This value reflects the residence time of the regionally deposited drug within the lumen. The extent of uptake from the airway into the lung tissue is defined by the fraction of the dose absorbed ($F_{\text{abs, lung}}$). This value reflects the extent of the initially deposited drug that is absorbed across the airway epithelium into the lung tissue. The luminal half-life and the fraction of the dose absorbed will be modeled using mechanistic PBPK software based on inputs of dose number (combined lung dose and solubility), and permeability (P_{eff}) and will be determined based on regional (central vs peripheral) and whole lung deposition dosing scenarios.

6. CONCLUSIONS

The utility of an iBCS as well as the basic principles and framework associated with the development of an iBCS have been proposed. Analogies between the iBCS and giBCS were explored, and the scientific basis and key product attributes of dose, solubility, and permeability were identified for both routes of administration. The fundamental principles used to mechanistically model dose, dissolution, and permeability and losses due to clearance mechanisms are route-specific. Therefore, time-based plug flow relationships used in the giBCS are not applicable to an iBCS.

Key differences between the proposed iBCS and the existing giBCS include the following:

1. The giBCS system focuses on systemic drug absorption and activity outside of the GI tract, whereas an iBCS system focuses on local drug availability within the lungs. However, since measurement of the regional drug concentration within the lungs is not yet easily achievable, systemic blood levels are typically used to monitor the pharmacokinetics of pulmonary drugs even though these blood levels represent downstream concentrations beyond the site of action for most drugs.

2. Mechanistic modeling of dissolution and absorption has been more extensively studied for orally administered drug products than for inhaled drug products. Mechanistic modeling of dissolution and absorption for inhaled drugs allows us to overcome the inability to measure luminal and lung drug concentrations.

3. The residence time in the giBCS is derived based on plug flow through a tube, whereas residence time within the lumen for inhaled drugs remaining will be dependent upon non-absorptive and absorptive clearance mechanisms as well as the physicochemical properties of the drug and the drug product. This fact, along with the limited understanding of the mechanisms associated with pulmonary drug retention, complicates the methods needed to determine iBCS absorption and dissolution numbers. Therefore, absorption and dissolution will be modeled mechanistically.

4. To avoid complications associated with tissue interaction (e.g., lysosomal trapping, tissue sequestration including macrophage uptake, and receptor site binding), as with the giBCS, the iBCS grid boundary separating high and low permeabilities will be determined based on absorption occurring via passive transcellular permeability discounting carrier-mediated active transport and drug metabolism.

5. The giBCS dose is the amount of drug in the oral dosage form, whereas an iBCS dose will be defined as the lung dose. The volume of fluid used to calculate the giBCS dose number is 250 mL. The lung lining fluid is not free-flowing, and the composition and volume are dependent upon the deposition location. However, the dose number as described by the giBCS can be used for the iBCS as long as a value for the volume available for solubilization of the deposited dose is defined.

It is envisioned that an inhalation-based biopharmaceutics classification system will provide formulators and discovery chemists working in the challenging and costly area of pulmonary drug delivery and product development with a product risk assessment tool that can inform decision-making and save development time and thus cost. An iBCS “Rule of Thumb” based on classification would therefore provide scientific approaches to mitigate CMC and clinical development risks based on biopharmaceutics and the anticipated lung doses.

In order to delineate the quadrants and boundaries of an iBCS grid, the impact of changes in inhaled drug product performance as described by dose number and permeability on the drug half-life in the lumen and the fraction uptake from the lumen into the lung tissue will need to be evaluated. These analyses will be discussed in a future publication.

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LIST OF ABBREVIATIONS

Al	Alveoli and alveolar ducts, generations 17–23
APSD	Aerodynamic Particle Size Distribution
Bb	The central airways, generations 0–16
BE	Bioequivalence
CF	Coarse Fraction, fraction deposited in the mouth-throat
C/P	Central to Peripheral deposition pattern
ELF	Epithelial Lining Fluid
Fabs	Fraction of the dose absorbed from the lungs
giBCS	Gastrointestinal Biopharmaceutics Classification System
GSD	Geometric Standard Deviation
iBCS	Inhalation-based Biopharmaceutics Classification System
IR	Immediate Release
MMAD	Mass Median Aerodynamic Diameter
PBPK	Physiologically Based Pharmacokinetics
Peff	Effective epithelial permeability
PQRI	Product Quality Research Institute
VMD	Volume Median Diameter

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NOTE ADDED AFTER ASAP PUBLICATION

This paper published ASAP on May 16, 2022, with an error in Figure 1. The corrected version was reposted on May 20, 2022.