The Utility of In Silico Modelling and Substitution Risk for Generic Orally Inhaled Drugs

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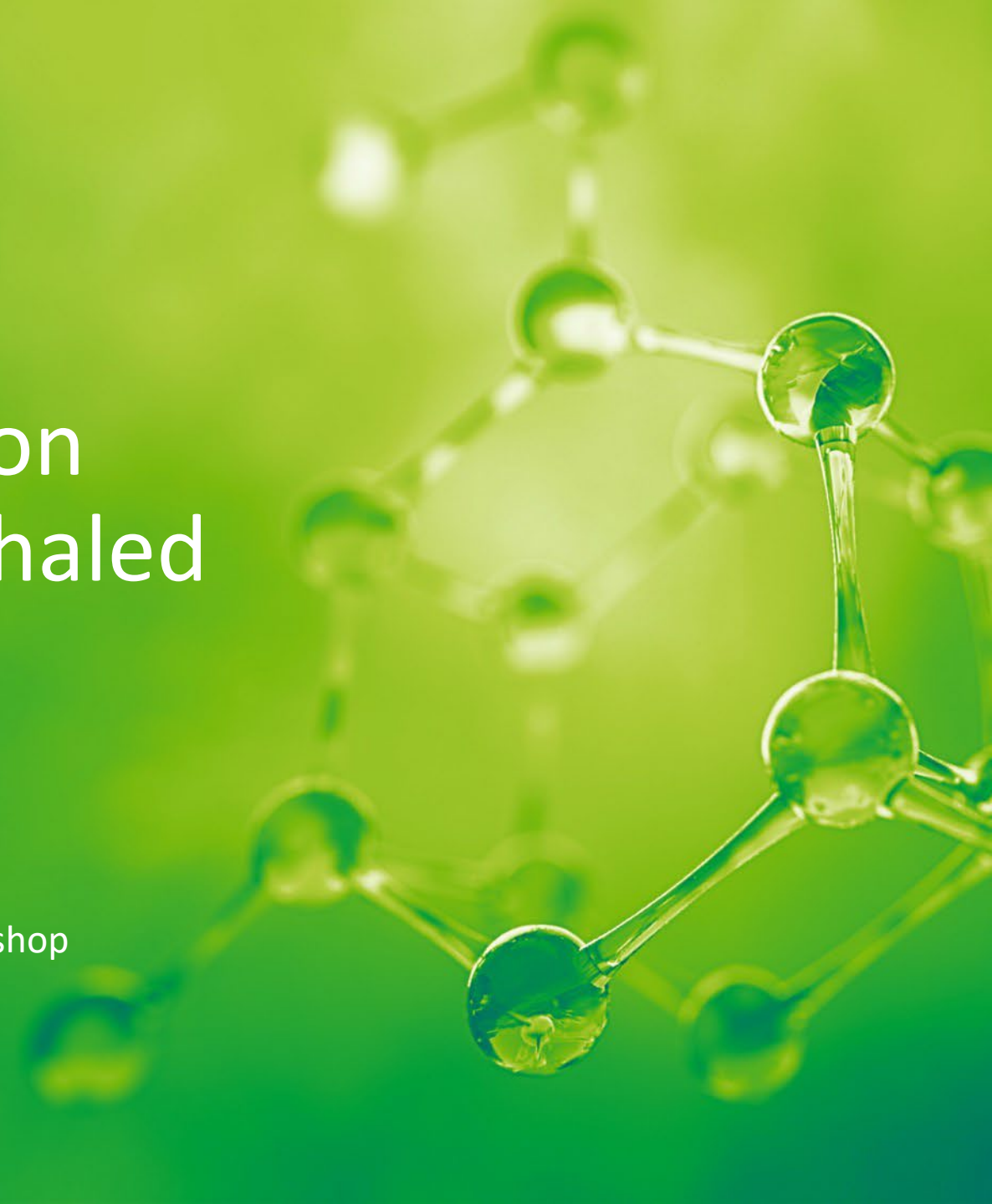

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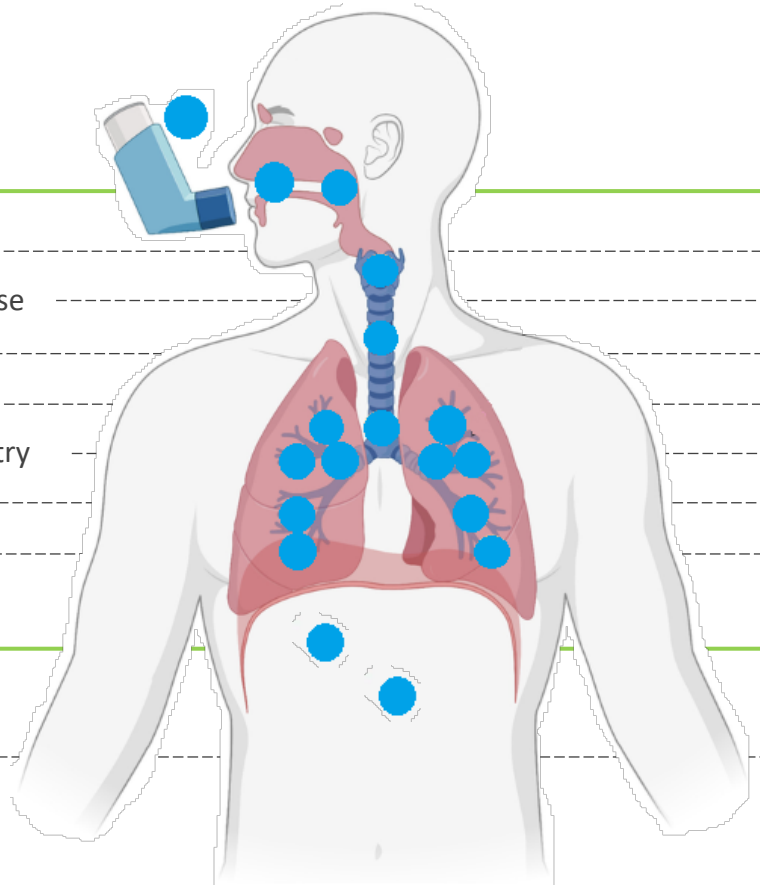
De-risking Performance Bioequivalence

Current BE for Q1/Q2 compliant generics can be demonstrated via ‘Option 1’ CE Waiver Approach

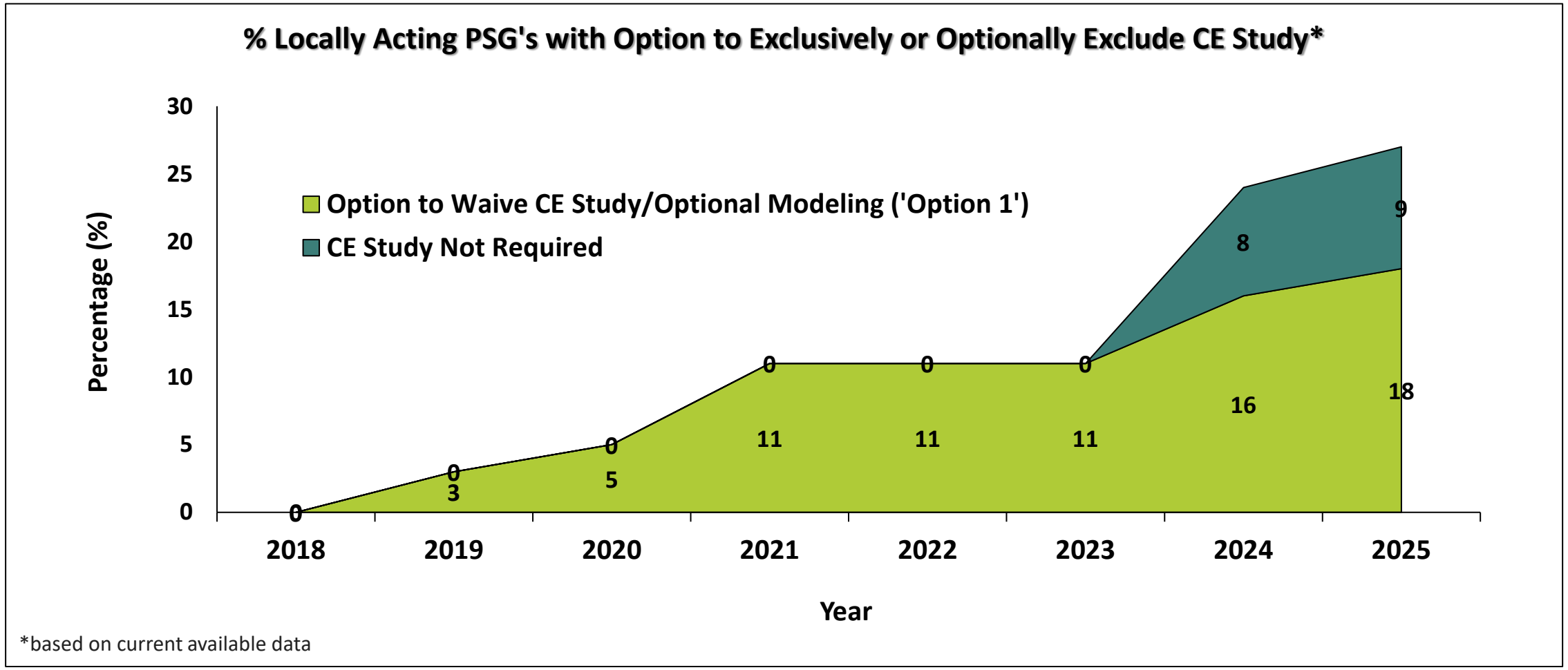


	Risk	Mitigation
Local Delivery	▪ Device	✓ Quality Engineering and ‘Use Steps Comparability’
	▪ Bolus Volume / Delivered Dose	✓ IVBE Dose Content Uniformity & (pMDI specific tests)
	▪ Inhalation Manoeuvre	✓ Appropriate Training
	▪ APSD Drug	✓ IVBE APSD (drug product)
	▪ Lung/Oropharyngeal Geometry	✓ IVBE Realistic APSD (rAPSD)
	▪ Microstructure (Q3)	✓ Characterisation of Emitted Dose
	▪ Dissolution	✓ IVBE Physiologically Relevant Dissolution
Peripheral Delivery	▪ Systemic absorption	✓ In silico PBPK assurance of BE ✓ Pharmacokinetic Bioequivalence

Adapted Image: Kumar, R., Mehta, P., Shankar, K.R. et al. Nanotechnology-Assisted Metered-Dose Inhalers (MDIs) for High-Performance Pulmonary Drug Delivery Applications. Pharm Res 39, 2831–2855 (2022)

Evolution of Product Specific Guidance's

A gradual launch of alternate BE and CE waiver options over the past 6+ years

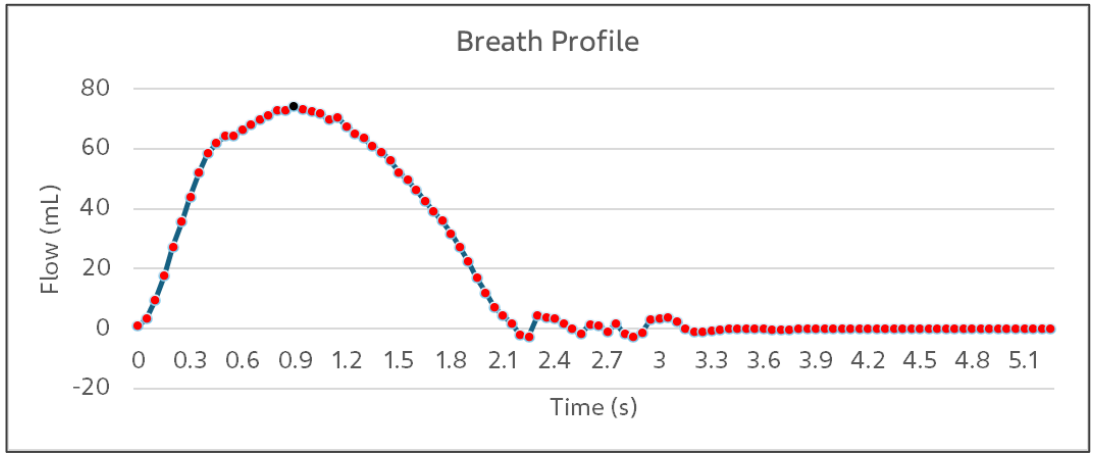


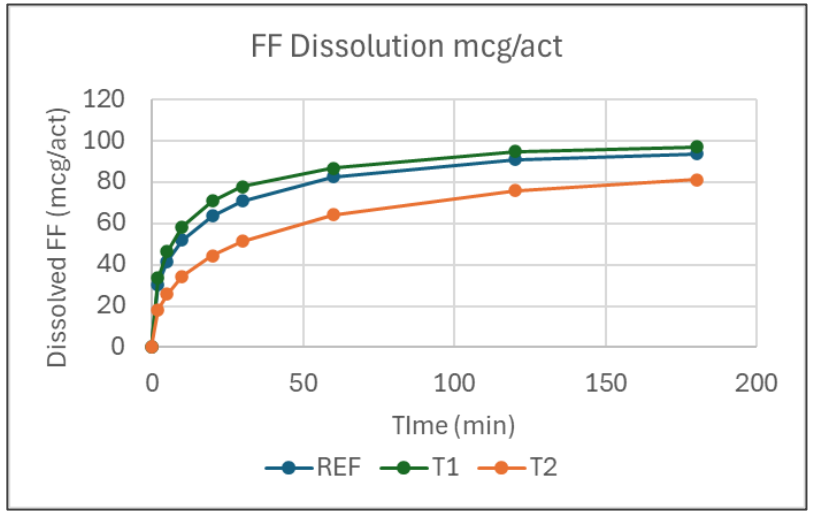
*based on current available data

PBPK Model Validation: Case Study

An assurance of clinical PK BE, expediting product development and generic product access

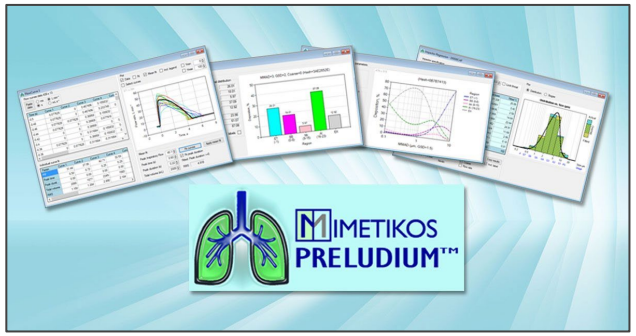
- **Preludium™ mechanistic PBPK model developed for a Fluticasone Furoate Dry Powder Inhaler**
  - Reference Product (REF)
  - Target Test Product (T1)
  - Differentially Performing Test Product (T2)
- **In Vitro Parameter Inputs**
  - **rAPSD**
    - Breathing profiles representing target population
    - Realistic MTs
  - **Dissolution**
    - Physiologically relevant method
- **Compartmental / Systemic Disposition Model**
  - Derived from literature IV study
  - Successfully Validated
- **Drug Independent / dependent Parameters**
  - Pulmonary regions, regional surface areas, ELF, tissue volumes, clearance rate etc. representing the Wiebel lung model.
  - Solubility, diffusion, density, molecular weight, etc.

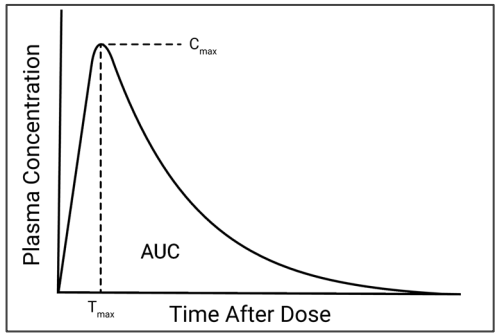




PBPK Model Validation: Case Study Cont.

An assurance of clinical PK BE, expediting product development and generic product access





Product	Predicted/Observed Ratio	
	AUC_{0-t}	C_{max}
REF	1.01	1.01
T1	0.94	1.06
T2	1.12	1.05

- ❑ PBPK Model for FF DPI successfully validated by comparing to *in vivo* PK data generated from same batches of test & reference products.
- ❑ Agreement in C_{max} and AUC values for predicted and observed PK – predicted/observed (p/o) ratios fell within 0.87-1.15.
- ❑ Validated PBPK models can enable right first time PK clinical outcome leading to timely generic drug availability.

Lung Deposition Modelling: Case Study

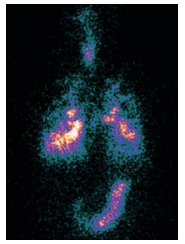
Significant validation challenge and uncertainty surrounding overall BE applicability

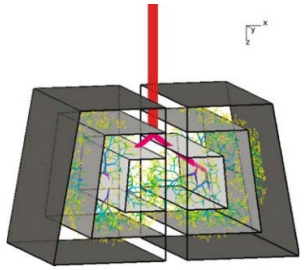
Objective alidate results of *in silico* semi-empirical regional lung deposition (Preludium™) model of inhaled tiotropium dry powder by comparison to a gamma scintigraphy study of inhaled radiolabelled Tiotropium dry powder.

Results

- C/P Ratios agree, BUT definitions of C and P regions of interest (ROI) differ; C/P Calculations not same.
- Literature: C and P regions only vs. Preludium™: definitions are those of Schroeter (includes intermediary region).
- To compare both study C/P ratios, an assumption must be made that the intermediary (I) region in literature study distributes to C and P regions in proportion to the contribution to C and P.

Parameter	Scintillation Study Healthy	Preludium™ Prediction Healthy	Scintillation Study Severe COPD	Preludium™ Prediction Severe COPD
C/P ratio	0.73	0.76	0.91	0.99





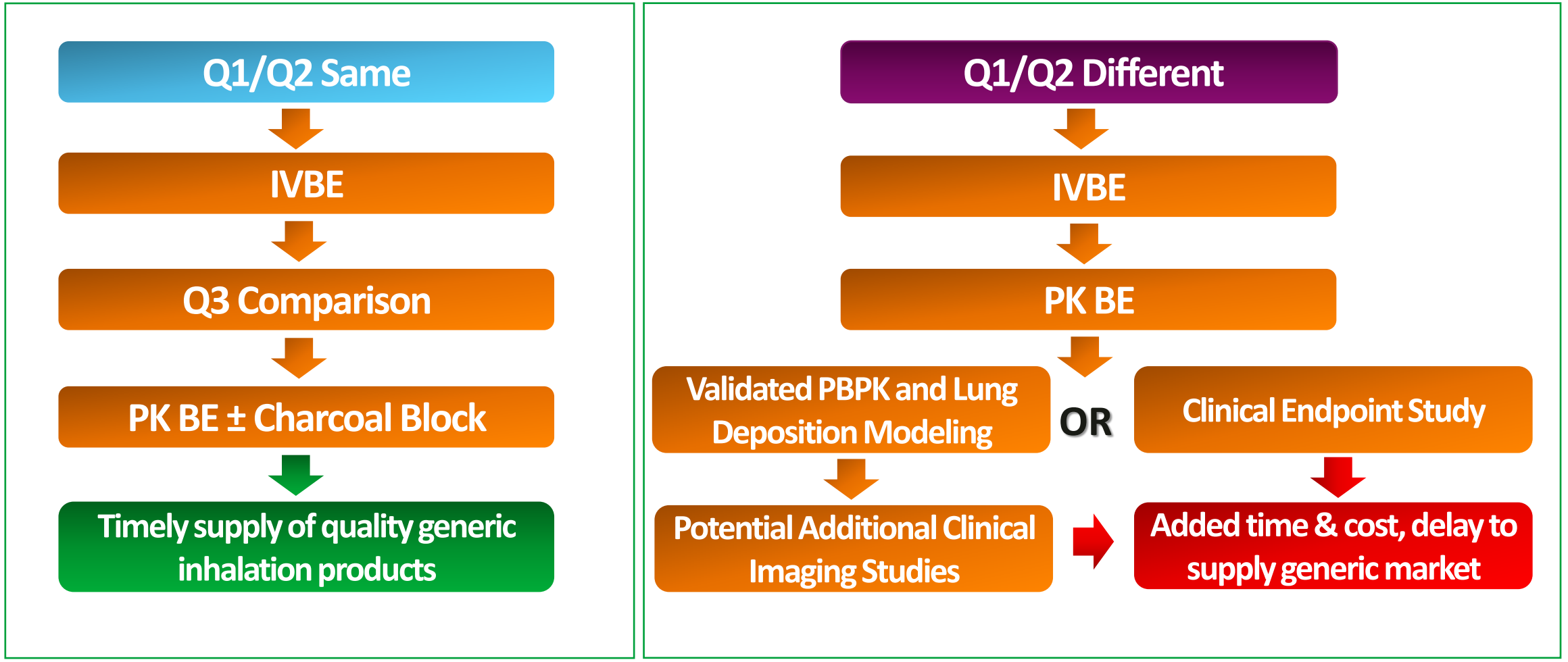
Challenge onducting further clinical studies (scintigraphy or other) adds to time required to develop product, and if validation were possible with assured comparable outcome, applicability of approach in terms of de-risking performance bioequivalence is unclear. PK BE could in fact provide assurance of systemic exposure sameness and assurance of local regional distribution sameness.

Research? What evidence could be provided to satisfy reliance on PK metrics as an assurance of regional lung deposition sameness between test and reference products?

Brand P et al. Lung deposition of radiolabelled tiotropium in healthy subjects and patients with chronic obstructive pulmonary disease. The Journal of Clinical Pharmacology. 2007;47(10):1335-41.
Schroeter et al. Airway identification within planar gamma camera images using computer models of lung morphology. Pharmaceutical research. 2005;22:1692-9.

Scope of the Generic CE Waiver Approach

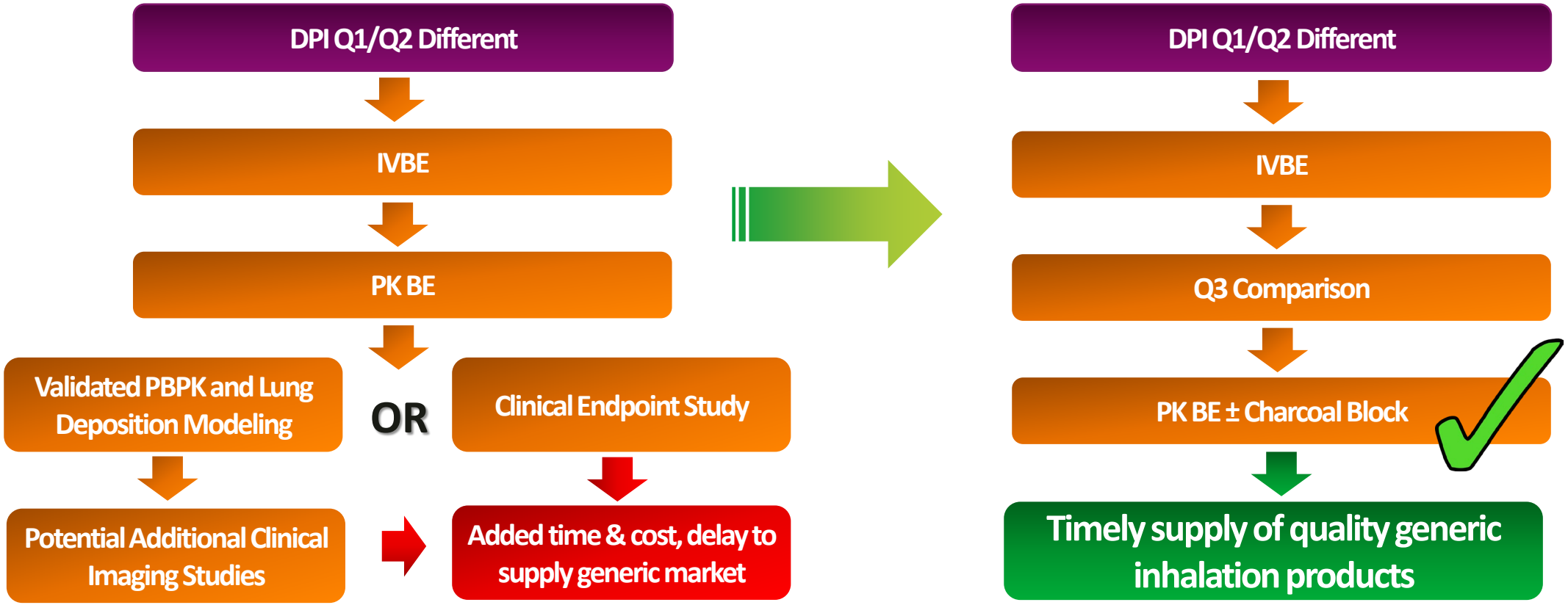
Could an 'option 1' CE waiver approach be extended beyond Q1/Q2 equivalence?



Scope of the CE Waiver Approach

Consider a risk based approach for Q1/Q2 differences?

If Q1/Q2 deviations do not affect the absorption of the active drug ingredient for products that are systemically absorbed, and do not significantly affect systemic or local availability for products intended to act locally, could an option 1 CE waiver approach be used?



Generic Device Design Considerations

Device improvements are limited by substitutability requirements/user steps

- Simplification and/or modification of device user steps can enable ease of use for patients and enhanced adherence to inhalation therapy
- User requirements for substitutability purposes limit the development of devices which could address a user challenge or serve an unmet patient need.

Summary & Concluding Remarks

- Risks associated with generic substitutability can be appropriately mitigated for Q1/Q2 complaint locally acting inhaled products using a CE waiver approach where the weight of evidence for BE relies on *in vitro* assessment, structural characterisation and systemic exposure (±CB).
- PBPK modelling can be successfully validated and virtual trials can serve as an assurance of BE prior to commencement of clinical PK studies, expediting the development process and generic access for patients.
- Validation of *in silico* lung deposition models is challenging given the lack of comparable *in vivo* data in the literature and conduct of imaging studies to potentially address this would add significant time to the development process, with no guarantee of regulatory acceptance or understanding of the associated BE risk mitigation. If via proof of principle, a validated lung deposition model can demonstrate that PK metrics are sensitive indicators of regional deposition pattern changes, can PK then be relied upon as a measure of local drug availability?
- Could Q1/Q2 non-compliant generics be considered as eligible for CE waiver so long as deviations do not affect absorption of the active drug ingredient for products that are systemically absorbed, and do not significantly affect systemic or local availability for products intended to act locally?
- Current substitutability criteria (user steps) can restrict the development of inhaled devices which could be improved to offer enhanced ease of use and patient adherence.


Thank you