CHECKLIST FOR PBBM REGULATORY SUBMISSIONS **Drug name/alias:** **Company name**: **Agency:**	
A)	**Identification of model objective/intended regulatory purpose**
Q1.	Does the report clearly describe the background and the intended model application /objective?
B)	**Model development**
Q2.	Is the strategy on model development described (preferably through flow chart or in stepwise write) up? *Description of modelling procedures, including model development, model validation/refinement, and model application. The procedures should be outlined in a stepwise manner using a workflow, decision-tree, table, or other representation. The model analysis should appropriately reference the data and studies used in each step of the modelling process*.
Q3.	Explain if *in vitro* data are able to discriminate critical product differences and *in vitro* methods are clinically relevant.
Q4.	Is PBBM model structure explained? *Description of mechanistic framework of drug oral absorption model (for example, ACAT/CAT/ADAM model) along with distribution model (minimal/full whole body PBPK) and elimination model (mechanistic IVIVE or classical compartment)*
Q5.	Are all drug model parameters enlisted, referenced, and justified where needed? • Physiochemical parameters (MW, LogD etc) • In vitro biopharmaceutic and formulation parameters (Permeability, solubility etc) • *In vitro*/*In vivo* DMPK/Clinical parameters (Vss, CL etc) *The approach taken to incorporate drug product quality attributes into the model and the selection of parameters and parameter values as model inputs should be clearly presented and scientifically justified. For example, impact of critical material attributes (CMAs) (such as drug substance physicochemical properties and excipient(s) level) and critical process parameters (CPPs) (such as compression force) on disintegration and in vitro dissolution as model*

	inputs should consider whether these attributes and parameters can affect drug in vivo dissolution and absorption. *All sources of drug parameter values should be clearly specified and justified (e.g., appropriate references). If there are several sources of one parameter, the justification of selection should be described. If a parameter value has been estimated, the data source and estimation method should be described or appropriately referenced. The use of clinical PK data to optimize model parameters should be described and justified.*
Q6.	Are the system parameters shared/available? • Proprietary software used (Gastroplus, SimCYP etc) • Population (demographics, physiology) *When library drug and system models (e.g., a virtual population) within a specific software platform are used, the sponsor should justify the use of these models and clearly identify and justify modifications made to the library models.*
Q7.	Is there acceptable justification for the approach selected for inputting dissolution data into the model (direct input vs. Z factor vs P-PSD etc) *Explanation from the sponsor provide explanation on the chosen dissolution model.*
Q8.	Is adequate clinical data available for model validation. If yes, is the clinical data used in model development clearly defined? *Clinical study data should be properly elucidated and appropriately referenced.* *Availability of IV and/or oral solution PK data to characterise the model* *Availability of reviewer checklist of various submitted files- model files, data files etc with clear information about its use in PBBM model to assist with model assessment*
Q9.	Are the model assumptions clearly stated? *The assumptions that underly the model structure and parameters should be clearly presented (e.g., the assumptions made upon drug product disintegration, dissolution, precipitation, degradation, transport, first-pass effect, distribution, and clearance). The assumptions should be scientifically justified with supportive information and data, as appropriate. The effect of these assumptions on model structure and/or parameter(s) should be described.*

Q10.	Is the virtual clinical trial or single simulation appropriate and does model analysis provide simulation design details?
C)	**Model validation**
Q11.	Does the analysis demonstrate that the proposed PBBM is appropriate for the modelling purpose or question asked for the drug product and study population and is robust enough to respond to perturbations in uncertain parameters? If not, assessors should provide a detailed explanation of what additional data would be needed for model validation *To demonstrate model predictive performance, sponsors should provide graphical and numerical comparisons of the predicted and observed in vivo drug concentrations (e.g., in plasma) versus time profiles as well as PK parameter estimates (e.g., Cmax, Tmax, and AUC) and statistical analysis of those estimates. Such statistical analyses are for example, average fold error (AFE), absolute average fold error (AAFE) or average absolute prediction error (AAPE%) e.g., (AFE, AAFE or AAPE%).* *Acceptance criteria for PBBM prediction performance (validation) should be defined and should be appropriate for the specified application. Use of cross-over or parallel study data and appropriate between subject variability may be stated if acceptance criteria are influenced by such variability in analysis.* *For example, for baseline PBPK, the predicted average PK profiles from a virtual population should not be statistically different from the measured ones across the studies selected for model validation. In general, for example for PBPK baseline model the predicted Cmax and AUC AFE should be comprised between 0.9 and 1.1, a maximal difference of 20% in the predicted Cmax and AUC as estimated by a PBPK model can be accepted (in line with IVIVC guidance) for cross over studies and the AAFE should be less than 1.25 and AAPE less than 25% for independent parallel studies (Appendix B).* *Failure to meet the predefined acceptance criteria should be discussed and consequences on model use should be defined. The reason for the mispredictions should be discussed if they are study specific. For example, high intrinsic PK variability for validation of baseline PBPK model). Another example could be an over-prediction of Cmax could be related to partial gastric emptying occurring in the clinic which was not well captured by the model if the model assumed a single-phase emptying. In this case, demonstration of the frequency of multiple peaks in the clinic and attempts to simulate partial gastric emptying with the PBBM should be presented to justify and explain the nature of the discrepancy. Approach used for inclusion of high between and/or within subject variability based on clinical data may be clearly defined and its likely impact on acceptance criteria of PBPK/PBBM model be stated.*

D)	**Sensitivity analyses**
Q12.	Is the model used to highlight the parameters most influential to absorption as determined by the use of sensitivity analyses and are those parameters well defined in the model? *Results of sensitivity analyses for main parameters influencing drug absorption should be presented. The value given to uncertain input parameters should be discussed in the context of the simulation conditions and potential clinical relevance. For example, PSA could be precipitation time on Cmax/AUC or permeability on Cmax/AUC.* The impact of other parameters (e.g permeability) on the sensitivity analysis results should be assessed.
12	**Model limitation(s)** Model limitations, uncertainty, and the impact on the model application should be discussed.
E)	**Model application**
Q13.	Does model analysis present the results of using the validated PBPK/PBBM to address the study question using tables, graphs, and text where appropriate? *Acceptance criteria for specific application should be defined and should be appropriate for the specified application. Appendix B enlists some common likely scenarios of PBBM applications and possible acceptance criteria for them.* *For example, to evaluate whether a dissolution method is biopredictive, PBBM analysis may incorporate dissolution profiles generated by such method into the PBPK model and the predicted systemic exposure should be comparable (±10 percent) to the observed in vivo PK data (a maximal difference of 20% in the predicted Cmax and AUC as estimated by a PBPK model can be accepted (in line with IVIVC guidance)*. *In general, BA would be considered unacceptable when, based on BE criteria, the 90 percent confidence interval of the test-to-reference geometric mean ratio of Cmax and AUC fall outside the range of 80 to 125 percent.* If/When virtual BE trials are conducted, the model estimated variabilities (between-subject variability and within-subject variability) should be sufficiently justified. Guidance on specific of different biopharmaceutic applications is provided in US FDA 'The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls Guidance for Industry'
Q14.	For intended application of PBBM, is there a need to define safe space and if yes, is safe space adequately demarcated?

	Safe space is defined by the boundaries demarcated by in vitro specifications (i.e., dissolution or, when applicable, other relevant drug product quality attributes), within which drug product variants are anticipated to be bioequivalent to one another.
F)	**Assessment of the overall model application**
Q15.	Do the results support the intended model application and arguments (e.g., dissolution specification, biowaiver, etc) as proposed by the modelers?

APPENDIX A: Metrics for determine predictive power of models.

These metrics can be applied to the PK parameters (observed and predicted) and to each datapoints in the PK profile.

- **Average fold error (AFE)** is defined by following equation:

$$AFE = 10^{\frac{1}{n}\sum \log\frac{Pred_i}{Obs_i}}$$

The AFE is an indicator of the prediction bias. A method that predicted all actual values with no bias would have a value of 1; Under-predictions are shown by an AFE below 1 and over-predictions by AFE values above 1. AFE values vary between 0 and infinity in general, a prediction may be considered satisfactory if the AFE is between 0.8-1.25, passable if AFE within [0.5-0.8] or [1.25-2], and poor if AFE within [0-0.5] or above 2.

- **Absolute average fold error (AAFE)** is defined by following equation:

$$AFE = 10^{\frac{1}{n}\sum\left|\log\frac{Pred_i}{Obs_i}\right|}$$

The AAFE converts negative log fold errors to positive values before averaging, measuring the spread of the predictions. AAFE values vary between 1 and infinity. A method that predicted all actual values perfectly would have a value of 1; one that made predictions that were on average 2-fold off (100% above or 50% below) would have a value of 2 and so forth. A prediction may be considered satisfactory if the AAFE was less than 1.25, passable if the AAFE was comprised between 1.25 and 2, and poor for AAFE above 2.

- **Average absolute prediction error (AAPE%)** is defined by following equation

$$AAPE(\%) = \frac{100}{n}\sum\left|\frac{Obs_i - Pred_i}{Obs_i}\right|$$

AAPE is measurement of prediction scaled to percentage units, which makes it easier to understand. It is very close quantitatively to (AAFE-1) *100

- **Percent prediction error (PPE%)** is defined by following equation

$$PPE(\%) = Geomean\left(\left|\frac{Pred_i - Obs_i}{Obs_i}\right|\right) \times 100$$

Appendix B. PBBM Applications and Proposed Risk-based Approach to Define Model Validation and Application Criteria.

Referenced from (IQ), I.C., *Comment from IQ for The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls.* IQ comments: https://www.regulations.gov/comment/FDA-2020-D-1517-0007

PPBM application	**Decision consequence (Low/Medium/High)**	**Model influence (Low/Medium/High)**	**Criteria for model validation**	**Recommended acceptance criteria for model validation**	**PBBM option for model application**	**Recommended criteria for model application**	**Conclusion/Comments on model application**
Demonstrate the biopredictive nature of the dissolution method using **cross over** study with individual fitting of disposition parameters for model validation	Low (dissolution method should show batch to batch consistency with level of discrimination)	Medium (model is based on clinical data)	PE %[A]	<10%	Not applicable	Not needed	If model valid, then dissolution method considered biopredictive
Demonstrate the biopredictive nature of the dissolution method using **independent parallel studies** for model validation and relying on geometric mean parameters (PK parameters and profiles)	Low (dissolution method should show batch to batch consistency with level of discrimination)	Medium (model is based on clinical data)	AFE for prediction of relevant clinical scenarios [B]	0.8-1.25	Not applicable	Not needed	If model valid, then dissolution method considered biopredictive
VBE to test different batches of drug product and waive clinical relative BA [C]	High (if safe space has not been established), Medium (if clinical data exist with similar batches)	Medium (model validation is based on clinical data)	AFE for prediction of relevant clinical scenarios [B]	0.8-1.25	VBE	GMR 90% CI between 0.8-1.25	Products considered bioequivalent, biowaiver granted
Define the size of the safe space (based on CQAs)	Medium (the knowledge space show clinical data where extreme variants were tested)	Medium (the knowledge space show clinical data where extreme variants were tested)	AFE for prediction of relevant clinical scenarios [B]	0.8-1.25	VBE	GMR 90% CI between 0.8-1.25	The edge of failure is defined for products or virtual products demonstrating bioequivalence to the reference product through VBE
					PSA	Min-Max predicted PK parameters	The edge of failure is defined for products or virtual products demonstrating differences higher

PPBM application	Decision consequence (Low/Medium/High)	Model influence (Low/Medium/High)	Criteria for model validation	Recommended acceptance criteria for model validation	PBBM option for model application	Recommended criteria for model application	Conclusion/Comments on model application
						within 20% of observed	than 20% of observed PK parameters
Justify the proposed specifications for CMA and CPP	Medium (the knowledge space show clinical data where extreme variants were tested)	Medium (the knowledge space show clinical data where extreme variants were tested)	AFE for prediction of relevant clinical scenarios [B]	0.8-1.25	VBE	GMR 90% CI between 0.8-1.25	The specification is defined for products or virtual products demonstrating bioequivalence to the reference product
					PSA	Min-Max predicted PK parameters within 20% of observed	The specification is defined when the CQA value tested lead to predicted PK parameters more or less than 20% of the observed reference PK parameters
Virtual BE and sensitivity analysis to predict within and between subject variability + Geomean exposure ratio and aid powering of future clinical trials	Low (since model informs future clinical trial in terms of subject size)	Low (model was validated on independent clinical data)	AFE for prediction of relevant clinical scenarios [B]	0.8-1.25	VBE and PSA	Not needed	The proposed study design should ensure that clinical objectives will be demonstrated, and that the product is safe to administer
LCM development: determine the target dose and release profile to improve product medical value (with PK-PD/PK-Tox models)	Low (the model is informative and clinical data will be generated for the LCM)	Low (the model is informative and clinical data will be generated for the LCM)	Not needed	Not needed	VBE or PSA	Not needed	Rationale could be presented in P.2 section
Get regulatory flexibility to change specifications within safe space	Low (safe space has been previously accepted	Low (safe space has been previously accepted	Not needed	Not needed	Not applicable	Not needed	If the safe space has been demonstrated, this change does not require additional modeling

PPBM application	Decision consequence (Low/Medium/High)	Model influence (Low/Medium/High)	Criteria for model validation	Recommended acceptance criteria for model validation	PBBM option for model application	Recommended criteria for model application	Conclusion/Comments on model application
If product batch dissolution is comparable (comply with f2) using biopredictive dissolution method = waive clinical BE evaluation [C]	Low (safe space has been previously accepted	Low (safe space has been previously accepted	Not needed	Not needed	Not applicable	Not needed	If the biopredictive nature of the dissolution method has been demonstrated
If batches show different dissolution with the biopredictive dissolution method (fail f2) but are shown to be BE in a virtual trial = Waive clinical BE evaluation [C]	Low (dissolution profiles are within safe space). High (dissolution profiles outside of safe space)	Low (dissolution profiles are within safe space). High (dissolution profiles outside of safe space)	Not needed	Not needed	Not applicable	Not needed	If the safe space has been demonstrated, this change does not require additional modeling: if the dissolution is comprised in the safe space, biowaiver is granted, if the dissolution is outside the safe space, the biowaiver is refused and clinical evaluation is required to extend the safe space if products are demonstrated bioequivalent

A: Percent prediction error : $PE = Geomean\left(\left|\frac{predicted_i - observed_i}{observed_i}\right| \times 100\right)$

B: Average Fold Error : $AFE = 10^{\frac{1}{n}\times\sum Log\left(\frac{predicted_i}{observed_i}\right)}$. AFE should be calculated for C_{max}, AUC, and the concentration time profiles for concentrations above a threshold of 0.1 x C_{max}

C: restrictions may apply for poorly permeable drugs based if changes concern excipients which can impact drug absorption