SimulationsPlus

Using GastroPlus, PBBM and PKPD to define dissolution safe space in support of registration specifications

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27th April 2023

Presentation Outline

1. Some definitions
2. Scientific & Regulatory landscape for PBBM
3. Regulatory and Industrial applications of PBBM
4. PBBM and PKPD : a winning team !
5. Acalabrutinib maleate tablet dissolution specifications setting

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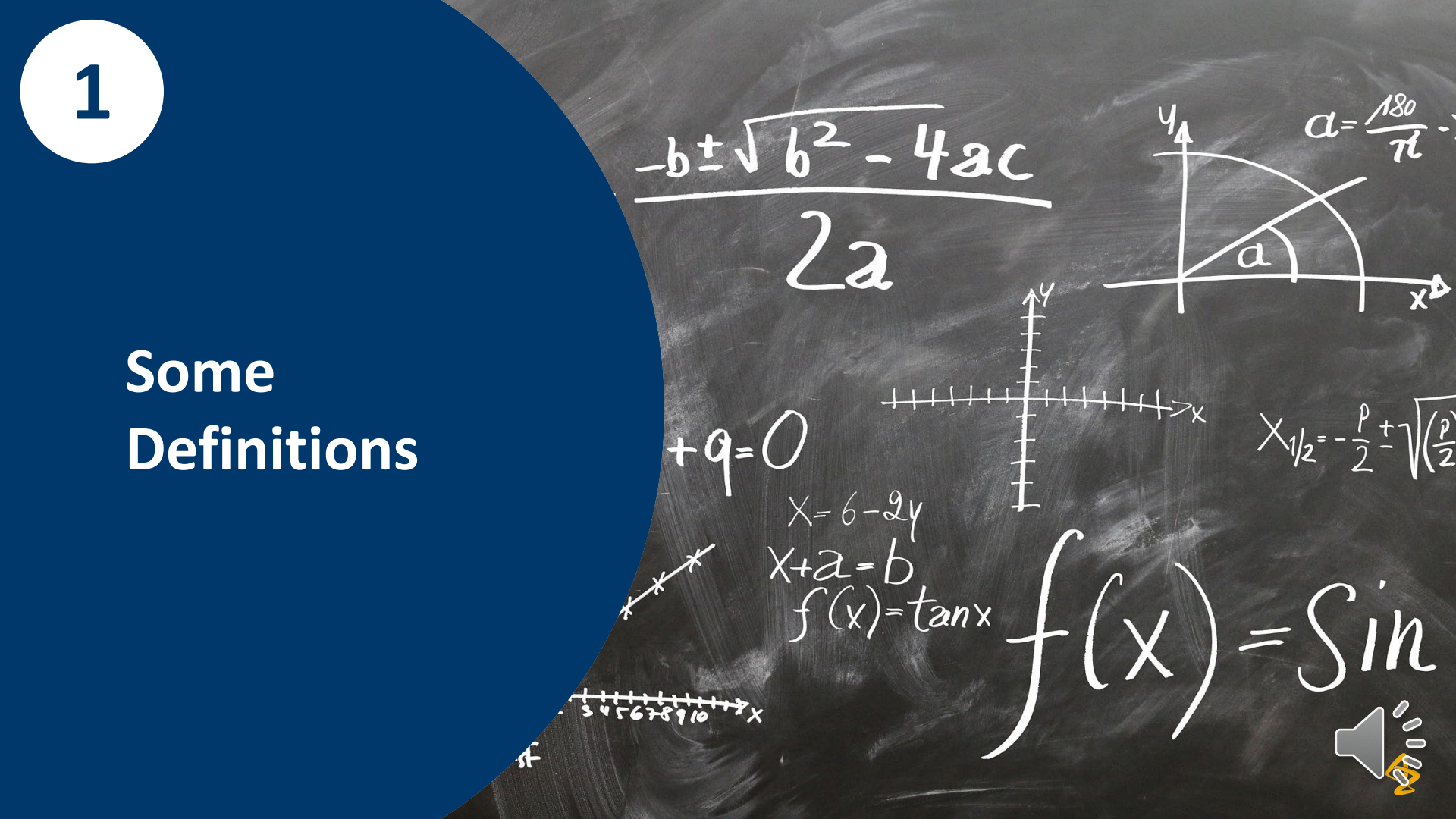
Some Definitions



Definitions

PBPK Model: Physiologically-Based Pharmacokinetic model

Describes the software tool. Agnostic to the use

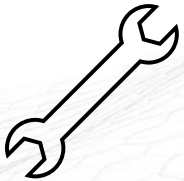
PBAM: Physiologically-Based Absorption Model

Focusses on drug absorption related parameters

PBBM: Physiologically-Based Biopharmaceutics Model

Fit for purpose application: Focusses on the use of the model to support biopharmaceutics/drug product quality applications

Graphical definitions



PBPK Model = the tool

The basis of PBAM and PBBM are PBPK models

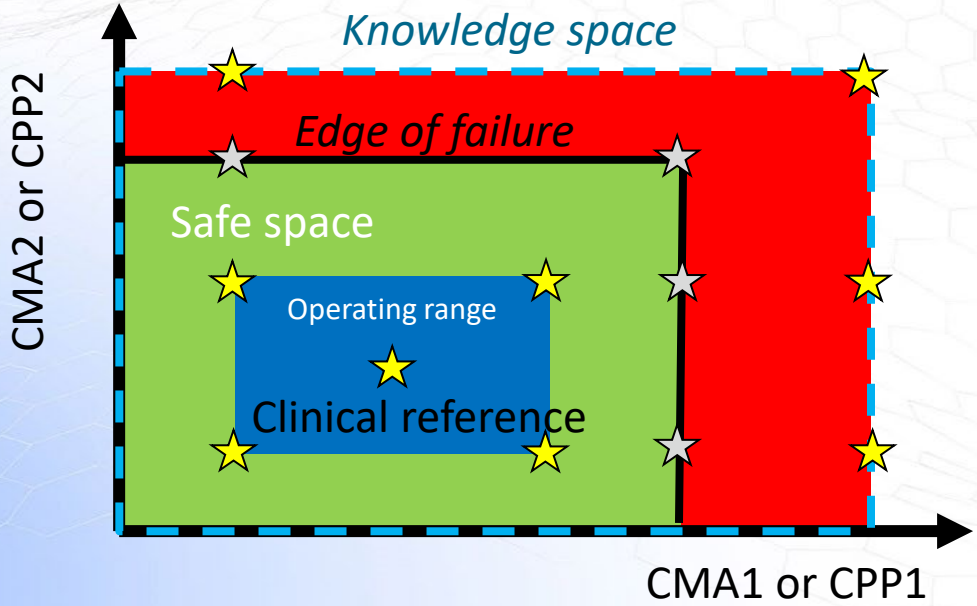
Objective

Understand limitations of drug absorption	Support drug product specifications (e.g., dissolution)	Waive human studies for DDI
PBAM	**PBBM**	**PBPK for DDI**

Use the right tool for the objective

The concept of safe space

Range of quality attributes for a drug product where all the batches manufactured are anticipated to be bioequivalent to one another



Knowledge space: Range of product QAs tested in the clinic

Operating range: Range of product QAs normally used for routine batch production

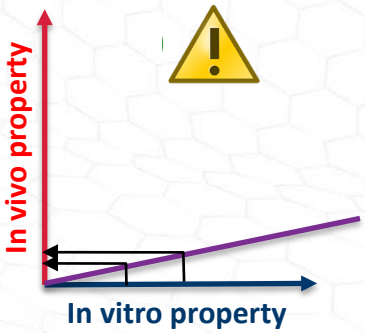
Clinical reference: DP Batch(es) used for pivotal studies

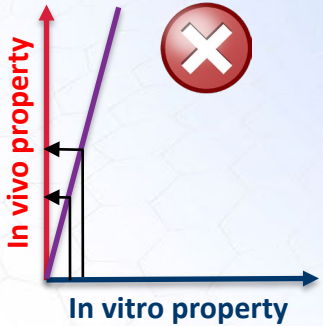
Edge of failure: Max QAs beyond which batches are not BE to clinical reference

Critical Biopharmaceutics Attribute (CBA): QA (CMA or CPP) which impacts exposure

Dissolution methods

Discrimination: changes in product in vitro performance are shown when CMA and or CPP are varied
Rank order: Changes in product in vitro performance align with in vivo behaviour





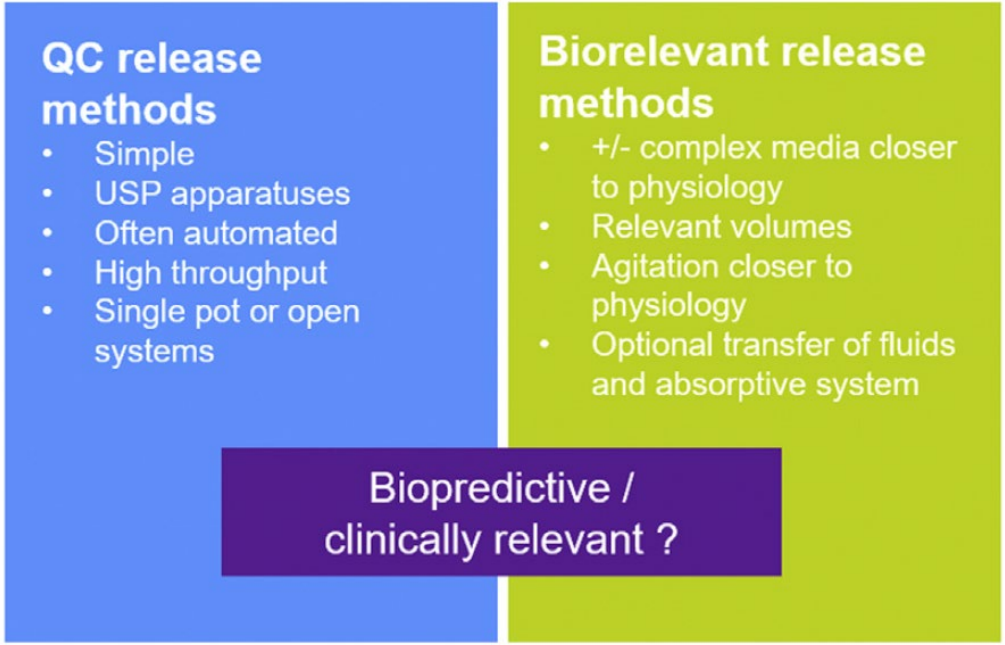
Right level : changes of in vitro properties translate to in vivo performance

Over discriminative: large changes in vitro translate to smaller changes in vivo

Under discriminative: small changes in vitro translate to larger changes in vivo

Both these methods may be clinically relevant and biopredictive

Dissolution methods



Biopredictive dissolution method A set of testing conditions for which in vitro dissolution profiles are capable of predicting pharmacokinetic profiles. These are typically based on classical or mechanistic IVIVC or PBBM.

Clinically relevant dissolution specifications A set of in vitro dissolution testing conditions and acceptance criterion(ia) that can identify and reject drug product batches that are not expected to be bioequivalent to clinical pivotal product batches.

Going further : Heimbach, T., et al., *Dissolution and Translational Modeling Strategies Toward Establishing an In Vitro-In Vivo Link—a Workshop Summary Report. The AAPS Journal, 2019.* ***21(2).***

https://doi.org/10.1208/s12248-019-0298-x

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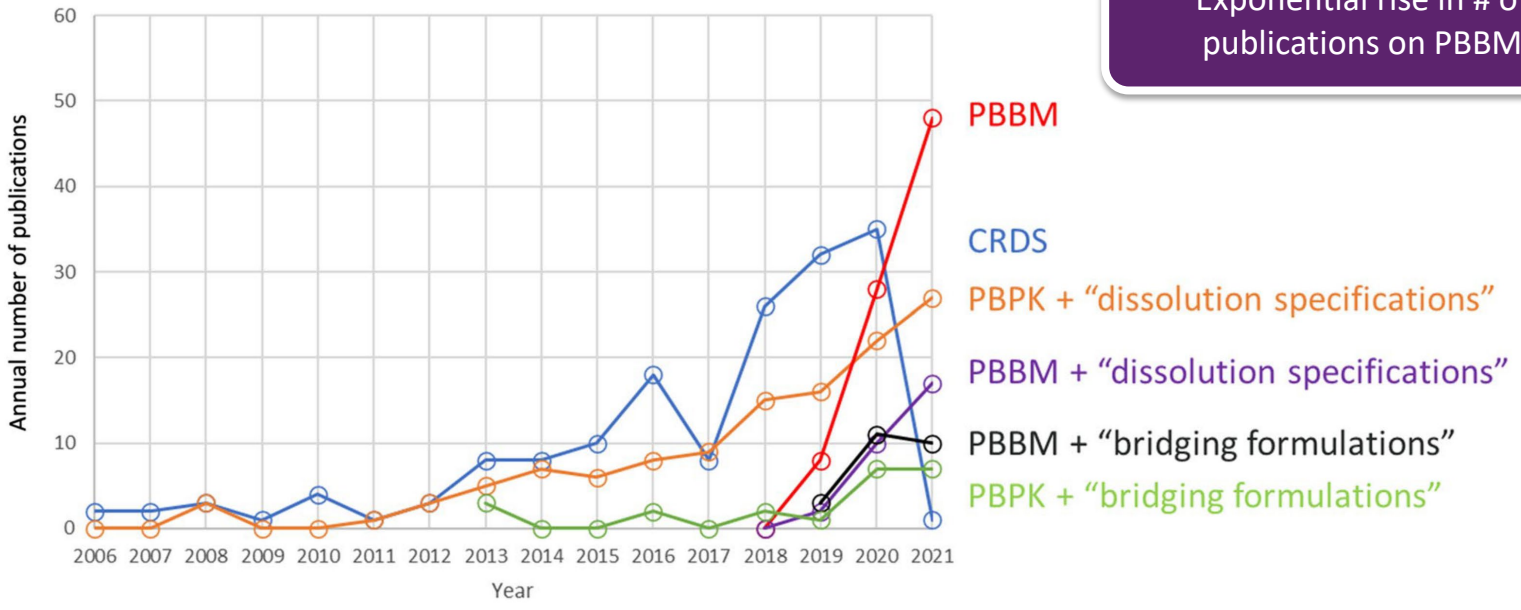
Scientific & regulatory landscape for PBBMs

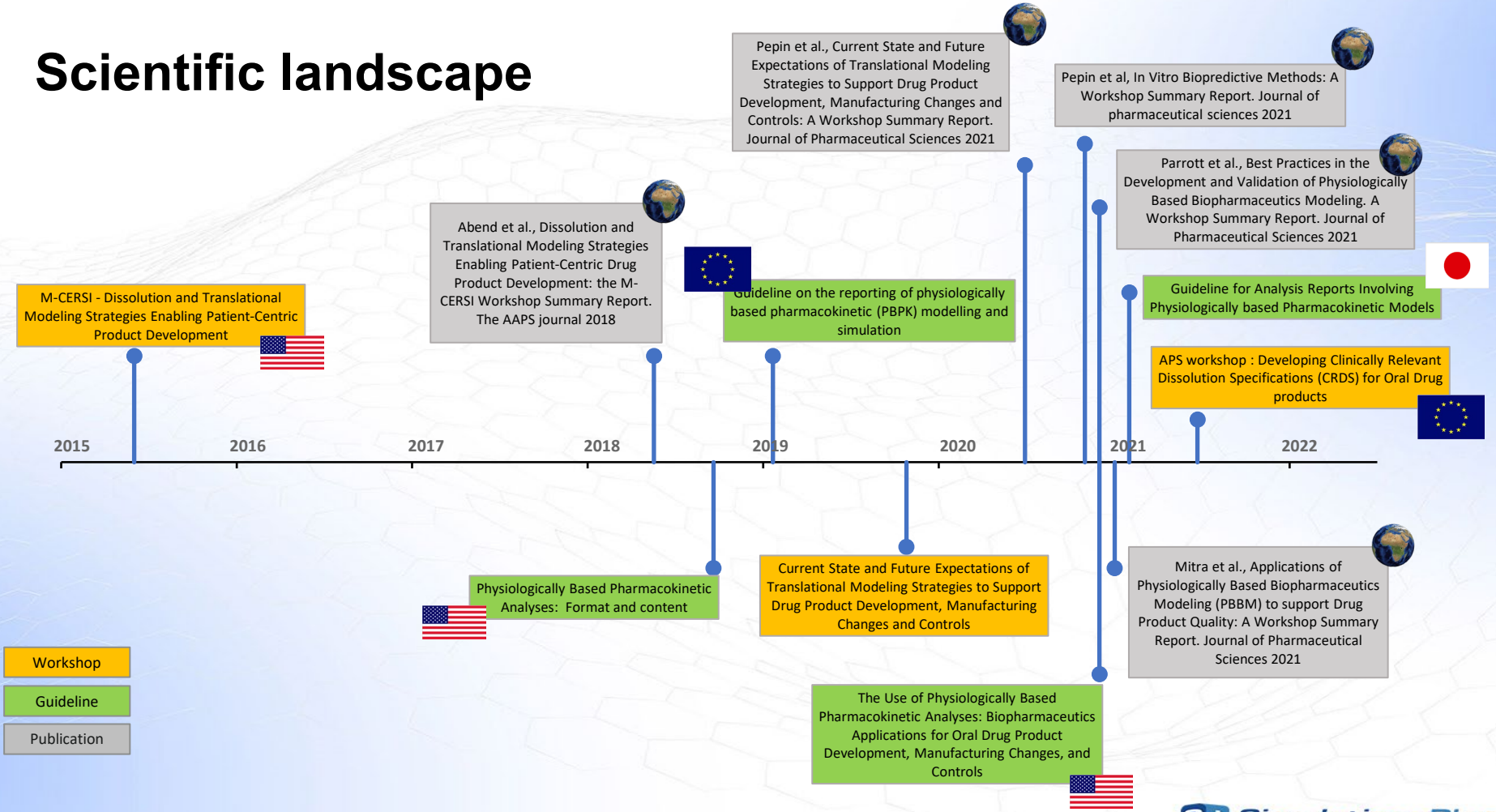
Scientific landscape



Exponential rise in # of publications on PBBM

Anand, O., et al., The Use of Physiologically Based Pharmacokinetic Analyses—in Biopharmaceutics Applications -Regulatory and Industry Perspectives. Pharmaceutical Research, 2022. https://doi.org/10.1007/s11095-022-03280-4

Scientific landscape



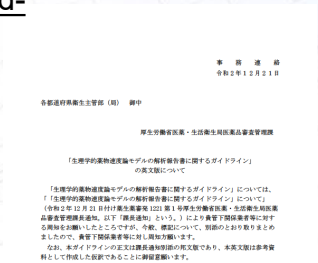
Regulatory landscape : Existing guidances

Model qualification (EMA only)
Model set-up
Model verification and modification
Model validation
Model use
Submission of model and all raw data (FDA only)

FDA guidance on : “Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry”
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/physiologically-based-pharmacokinetic-analyses-format-and-content-guidance-industry

EMA guideline on : “Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation”
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf

JP guidance on: “Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models”



事 務 連 絡
令和２年１２月２１日

各都道府県衛生主管部（局） 御中

厚生労働省医薬・生活衛生局医薬品審査管理課

「生理学的薬物速度論モデルの解析報告書に関するガイドライン」
の英文版について

「生理学的薬物速度論モデルの解析報告書に関するガイドライン」については、「「生理学的薬物速度論モデルの解析報告書に関するガイドライン」について」（令和２年１２月２１日付け薬生薬審発１２２１第１号厚生労働省医薬・生活衛生局医薬品審査管理課長通知。以下「課長通知」という。）により貴管下関係業者等に対する周知をお願いしたところですが、今般、標記について、別添のとおり取りまとめましたので、貴管下関係業者等に対し周知方願います。

なお、本ガイドラインの正文は課長通知別添の和文版であり、本英文版は参考資料として作成した仮訳であることに御留意願います。

Model application focussing on biopharmaceutics

The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-physiologically-based-pharmacokinetic-analyses-biopharmaceutics-applications-oral-drug-product

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Regulatory and industrial applications of PBBM

Benefits of PBBM

Mechanistic understanding → increase product value	Limitations to drug absorption (solubility, permeability, dissolution rate…) → guide formulators for 1st time right or LCM, Acceptable content of excipients,
Clinically relevant design spaces	Edge of failure for Critical Material Attributes and Critical Process Parameters
Justify drug product specifications	Enables the establishment of CRDPS
Support PACs	At submission, only a limited # of batches are manufactured. Product and process performance my deviate from initially filed specifications
Regulatory flexibility	Change in specifications: Flexibility granted within the safe space
Biowaivers	Reduction of unnecessary human testing. Best use of clinical resources combined with modelling and simulation

PBBM reduces the need for clinical trials and allows to optimize the clinical resources/timing, increase mechanistic understanding and allows informed decision making

Typical savings of PBBM along the value chain

Mechanistic understanding → increase product value

Quality by design : Reduce the time to market.
Avoid bridging between phase 1-3 formulations

1-2 year per project

Clinically relevant design spaces

Justify drug product specifications

Support PACs

Ensuring manufacturing ability:
Increase yield, reduce wastage

5-10 percent annual yield increase

Answer regulatory authorities questions at time of submission: (e.g. validation campaign to redo, clinical evaluation and its reporting) + 6 Month of market value 10-15 mUSD per project

10-15 mUSD per project +6 months

Regulatory flexibility

Biowaivers

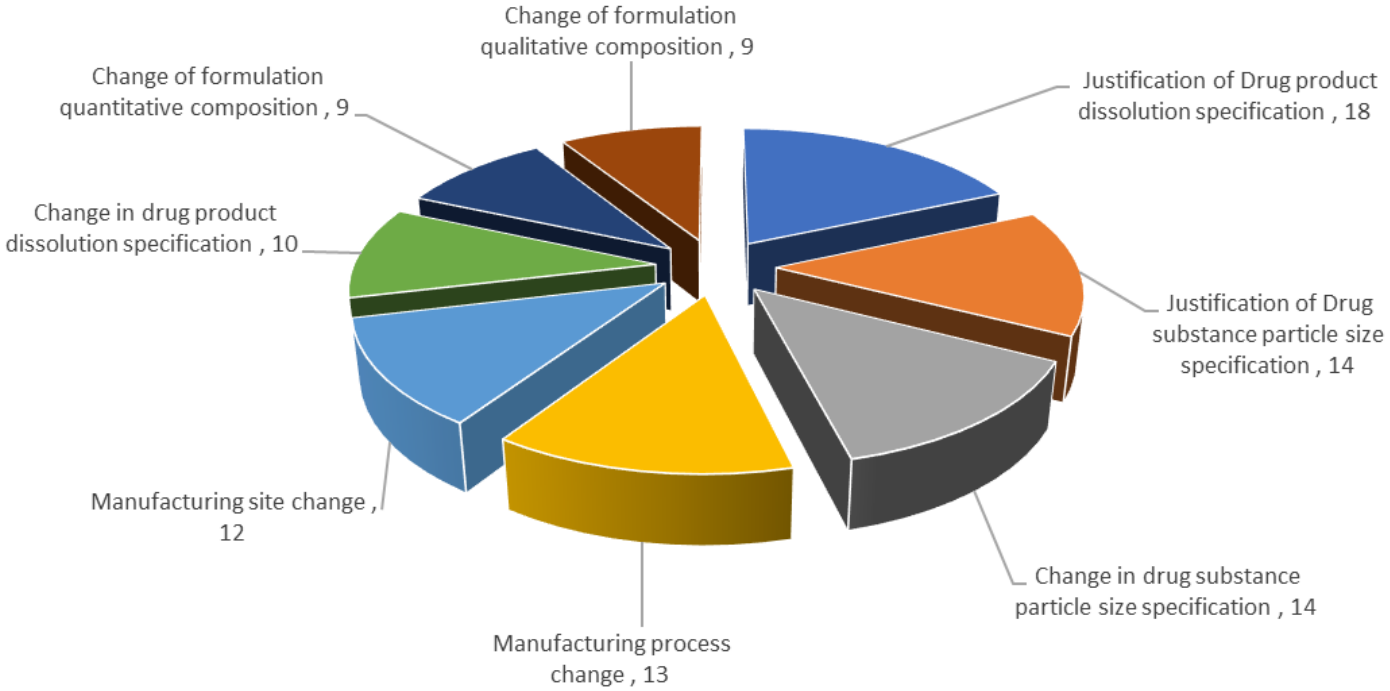
Typical BE study costs: variable if healthy volunteers or patients

1-10 mUSD per study +6 months

Total savings per project : up to 3-4 years time = sales 10% increase in yield and 20-30 mUSD savings

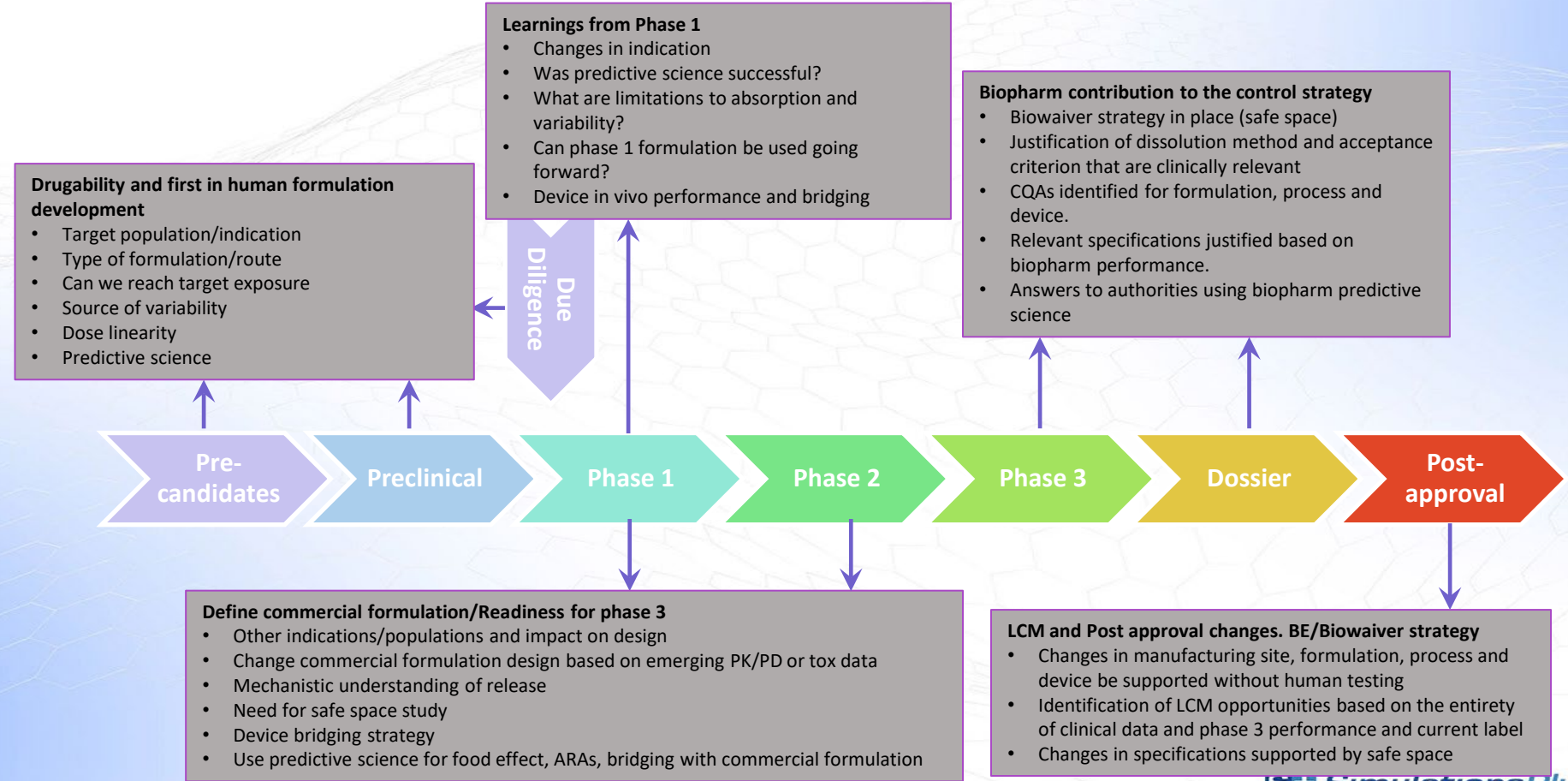
Objectives of PBBM

Uses cover R&D and PAC applications



Mitra, A., et al., Applications of Physiologically Based Biopharmaceutics Modeling (PBBM) to support Drug Product Quality: A Workshop Summary Report. Journal of Pharmaceutical Sciences, 2021. 110: p. 594-609. https://doi.org/10.1016/j.xphs.2020.10.059

PBBM in the pharmaceutical industry



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PBPK and PBBM: A winning team !

Why PBBM and PKPD ?

- PBBM links drug product quality attributes to in vivo exposure
  - In vitro drug product dissolution
  - Drug substance particle size distribution
  - Polymorphic impurities
  - Manufacturing process and material attributes (through dissolution)
  - In vivo degradation
  - Effect of excipients on solubility, dissolution, precipitation or on the GI function

PBBM allows a safe space definition where all drug product batches are anticipated to be bioequivalent to one another

Typically, virtual bioequivalence studies are conducted with standard, or reference scaled BE criteria, to conclude on bioequivalence

The size of the safe space is bound by the bioequivalence criteria

Why PBBM and PKPD ?, cont.

- PKPD links drug product exposure to efficacy and safety
  - They are based on observed efficacy data vs exposure (clinical endpoint or biomarkers of efficacy)
  - They can be mathematical relationships based on observations or mechanistic models based on the understood mechanism of action and cell signaling pathways

PKPD models allow to define an effective (and safe) space where all the batches are anticipated to have the same pharmacological efficacy without safety issues

Larger than bioequivalent bound safe spaces may be accessible through PKPD modeling

Combination of PBBM and PKPD links product quality attributes to efficacy/safety

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Acalabrutinib maleate tablets : Justification of Clinically Relevant Drug Product Specifications