Health Canada Santé Canada

Canada

PBBM in Regulatory Submissions at Health Canada

PBBM Best Practices to Drive Drug Product Quality:
Regulatory and Industry Perspectives

August 29 – 31, 2023

Shereeni Veerasingham, MBBS, PhD

A/Manager, Division of Biopharmaceutics Evaluation 3
Bureau of Pharmaceutical Sciences
Pharmaceutical Drugs Directorate

Disclaimer

The scientific views and opinions expressed in this presentation are those of the speaker and do not necessarily represent the policy or recommendations of Health Canada.

Policy Statement on Pharmacometrics

Pharmacometric approaches are an evolving tool used throughout drug product development, to gain regulatory approval, and for drug product life cycle management.

In 2021, Health Canada published a Policy statement:
Use of pharmacometrics in drug submissions and clinical trial applications.

- Informs sponsors of the principles to consider when filing drug submissions and clinical trial applications that use pharmacometrics approaches.
- The extent to which pharmacometric analyses may inform a regulatory decision is based on:
    - the quality of the data and analyses
    - the strengths and limitations associated with their use
    - the feasibility of alternative conventional approaches

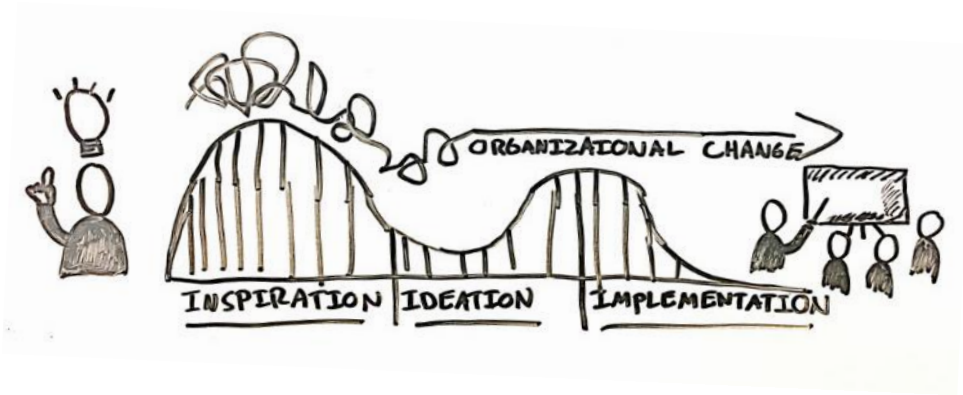
Health Canada is participating on ICH M15: General Principles of Model Informed Drug Development.

BPS Organisational Change – DBE3 Pilot

Submissions increasingly include evolving methodologies, such as biopharmaceutics modelling, as alternative bioequivalence approaches and to support risk assessments for drug product quality.

In September 2022, BPS implemented an organisational change by creating a pilot team, DBE3, to respond to the increase in complex and evolving areas of biopharmaceutics review.

- Dedicated resources for scientific issues that impact evolving methods and complex products.
- Centralised expertise for biopharmaceutics modelling evaluations within BPS, co-located with Quality. Other modelling (PBPK, PopPK, PK/PD) is reviewed by the Pharmacometrics team, BPSIP.



BPS: Bureau of Pharmaceutical Sciences; BPSIP: Bureau of Policy, Science and International Programs

Regulatory Applications of Biopharmaceutics Modelling

Waivers of the requirement to provide *in vivo* bioequivalence data (biowaivers) to support:

- Bridging of formulations during the clinical program, or to the commercial formulation
- Additional strength(s), when bioequivalence for one strength is supported by clinical data
- Changes to manufacturing process or site(s), scale-up of batches for production

Biopredictive dissolution methods:

- Appropriate *in vitro* dissolution conditions for extended-release/ low solubility products
- *In vivo* relevance of dissolution method for complex drug products, *e.g.*, long-acting injectables

Safe-space designation for manufacturing controls:

- Justify drug or product specifications and acceptance criteria

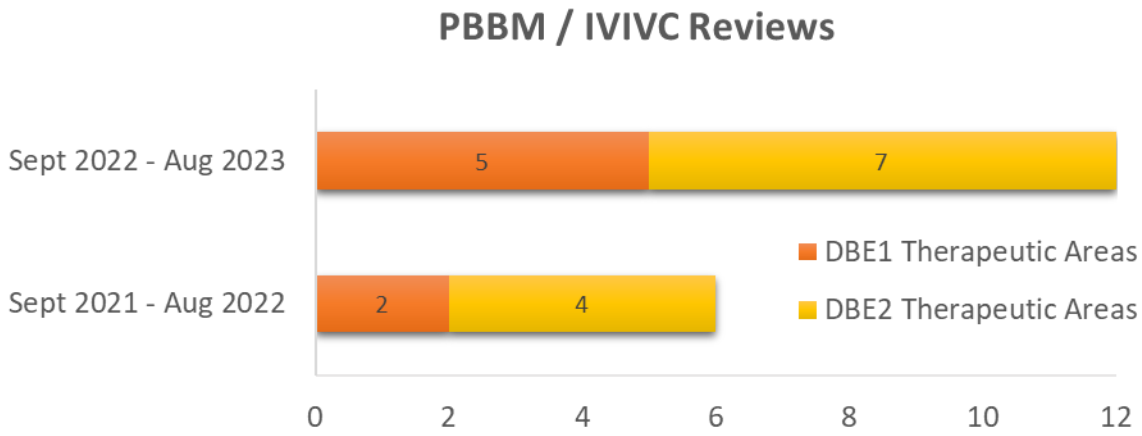
Increase in Submissions with Biopharmaceutics Modelling

Sept 2022 – August 2023, DBE3 reviews:

- 2-fold increase in submissions
- Reflects growing applications of PBBM

External engagement:

- Pre-submission meetings
- Industry association meetings
- Presentation at CSPS/ CC-CRS Annual Symposium, Toronto, May 2023



PBBM/ IVIVC submission reviews, completed and ongoing from September 2021 – August 2023, presented as 12-month periods.

CSPS/ CC-CRS: Canadian Society of Pharmaceutical Sciences/ Canadian Chapter – Controlled Release Society

DBE1 therapeutic areas: non-prescription, anti-Infective, cardio-renal, gastroenterology, anti-virals, allergy, and respiratory
DBE2 therapeutic areas: central nervous system, reproduction, urology, anti-neoplastic, metabolic, and musculoskeletal

Streamlined Review Process

DBE3 review process:

- Submission screened and assigned to review divisions
- Review teams: scoping, kick-off meeting (major deficiencies, information request issued).
- Progress meetings and discussion/ consultation with other teams (quality, pharmacometrics, clinical).
- Director briefing to finalise recommendation for submission.

Evaluations are considered case-by-case, with consideration for the context of use, and available guidance (*e.g.*, FDA draft guidance on PBPK analyses for biopharmaceutics applications).

PBBM filing within eCTD:

- Summary in module 2.7.1: Summary of Biopharmaceutics Studies and Associated Methods
- Reports in Module 5.3.1.3: *in vitro – in vivo* correlation, file tag: PBBM report
- Review template to facilitate PBBM evaluation, provided during screening/ initial review
- Planned: revision to Abbreviated New Drug Submission checklist to identify modelling data

Concerns Noted for PBBM in Submissions

Model development

- Model objectives are not clearly defined
- Input parameter values are not adequately justified
- Uncertainty in parameter estimates is not adequately addressed
- Dissolution data input method is not discussed/ scientifically justified
- Limitations are noted during development, but refinements were not considered

Model validation

- Model validation datasets are not appropriate or are inadequate
- Validation criteria are not stated *a priori*

Model application

- Variability is not mechanistic/ adequately incorporated in the virtual trial population.
- Model risk and feasibility of alternative approaches is not discussed.

Take-home Messages

A carefully considered modelling strategy and a well-organised, detailed PBBM report facilitates evaluation.

- Checklist for PBBM Regulatory Submission is a useful tool

Continued interaction and collaboration with other regulators, industry, and academia is required to further regulatory application of PBBM.

Planned engagement:

- Virtual seminar series
- PBBM workshop at Ottawa, 2024

Acknowledgements

- Arthur Okumu, Clinical Assessment Officer, DBE3
- Chris Rose, Director, BPS

shereeni.veerasingham@hc-sc.gc.ca