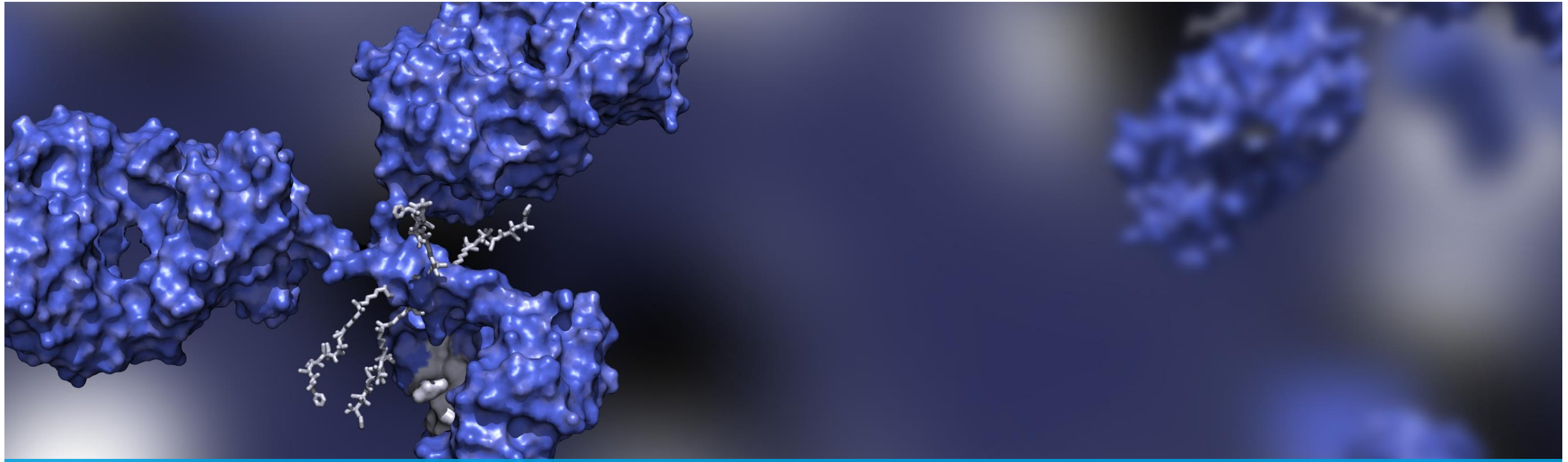

Application of Virtual BE Trials to support formulation bridging

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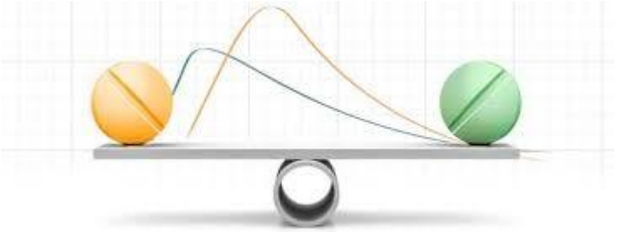
FDA/M-CERSI Physiologically Based Biopharmaceutics Modeling, PBBM Best Scientific Practices to Drive Drug Product Quality: Latest Regulatory and Industry Perspectives
Aug 31st 2023

Antibody drug conjugate with four drug compounds linked to IgG immunoglobulin

Agenda

1. **VBE – Recap**
2. **What could be covered under formulation bridging?**
3. **Examples 1 & 2**
4. **Points to consider**

VBE - Virtual Bioequivalence



Quick Recap

- BE is used to assess the comparison of relative bioavailability between two products containing the same API
- Usually assessed through a PK comparison in a clinical study (with clear guidelines and acceptance criteria)
- **V**BE is when BE is demonstrated using modelling and simulation in place of a clinical study
- Can save time and money ☺

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VBE - Virtual Bioequivalence

Areas of potential application

- BE studies are often performed in 3 main areas
  - Change in Manufacturing site (site switch)
  - Creating/introducing a new formulation
  - Introduction of a generic drug product

- Creating /introducing a new formulation can include studies to
  - Bridge between 2 formulations
  - Evaluating the Food effect
  - Evaluate any PPI effect (the CMC DDI ☺)
  - Setting of Clinically Relevant Specifications

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Springer link

VBE - Virtual Bioequivalence

Formulation Bridging

- Which APIs/DPs could qualify for formulation bridging
  - Depends on timing of bridge – pre, post or during pivotal studies
    - Scientific and/or regulatory risk?
  - BCS I and BCS III API
    - Is the level of change covered through ICH M9?
- Type of bridging often done in Industry through clinical studies
  - Liquid to solid
  - Solid to solid (capsule to tablet)
  - Change in excipient (outside ICH M9 for BCS III or SUPAC BCS II/IV)
  - Change of platform (conventional to enabling)
  - Exploration of drug product CQAs

Easy Drawing Guides

VBE – Virtual Bioequivalence

Example 1 – Mechanistic absorption modelling to assess the impact of drug product changes on the exposure of JNJ-X

- BCS II
- API in capsule for Ph 2 POC then acceleration to Phase 3 with a final tablet
- Tablet changes include:
  - API synthesis
  - Increase in lubricant
  - Change of non-functional coat
- Modelling used for internal drug product de-risking

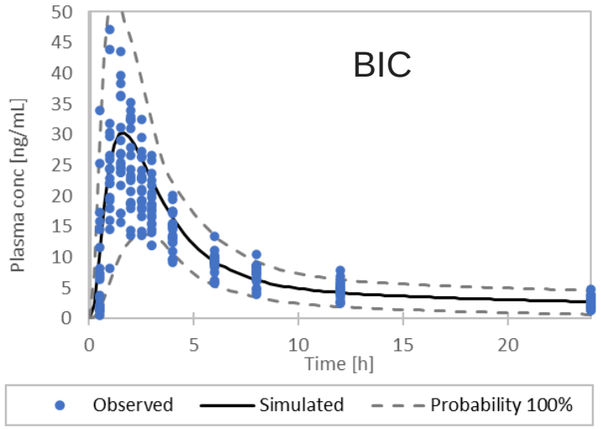
VBE – Virtual Bioequivalence – Example 1

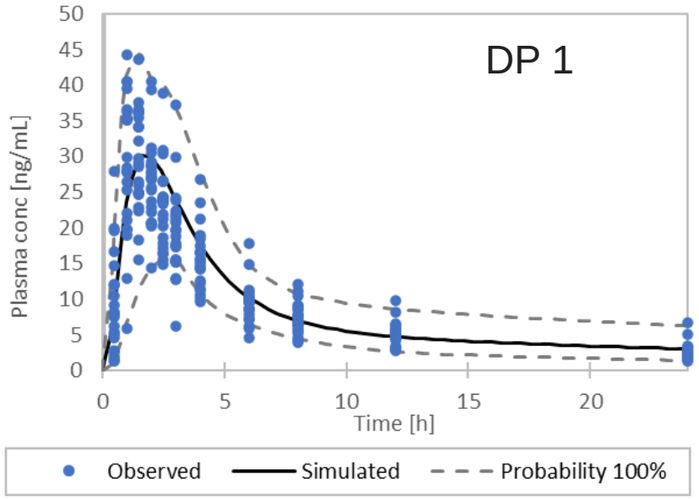
Steps taken in model building

- Oral absorption model development
  - DS
  - DP
- PK Model Development
- Parameter Sensitivity Analysis
- Model Validation
  - Independent clinical datasets
- Model Application
  - Comparing different formulations through VBE

VBE – Virtual Bioequivalence – Example 1

Model verification & VBE out come





DP 1 vs DP 2	C_{max}		AUC_{inf}		BE Criteria
	GMR	90% CI GMR	GMR	90% CI GMR	
	[-]	[-]	[-]	[-]	[-]
Study 1	0.95	0.86-1.04	1.03	0.91-1.16	0.8-1.25
Study 2	0.96	0.87-1.05	1.04	0.93-1.16	0.8-1.25
Study 3	0.95	0.85-1.05	1.00	0.90-1.10	0.8-1.25
Study 4	1.04	0.92-1.17	1.03	0.91-1.17	0.8-1.25
Study 5	1.05	0.94-1.17	1.02	0.92-1.13	0.8-1.25
Study 6	1.06	0.97-1.17	0.98	0.86-1.12	0.8-1.25
Study 7	0.93	0.84-1.03	1.03	0.92-1.14	0.8-1.25
Study 8	1.05	0.96-1.16	0.97	0.86-1.09	0.8-1.25
Study 9	0.98	0.89-1.08	0.98	0.87-1.09	0.8-1.25
Study 10	1.05	0.96-1.15	0.99	0.90-1.08	0.8-1.25
Mean	1.00		1.01		

- VBE trials demonstrate both drug products @ dose A are predicted to be BE for both C_{max} and AUC.
- A switch from DP 1 to DP2 is predicted to have no impact on absorption and exposure

VBE – Virtual Bioequivalence

Example 2 – Mechanistic absorption modelling to assess the impact of changes in API polymorph on the exposure of JNJ-Y

- BCS IV
- Immediate release tablet commercially available
- New crystalline form appeared (continuous process improvements)
- VBE used as part of a biopharmaceutical risk assessment to evaluate whether there could be any differences between the forms that may influence in vivo performance

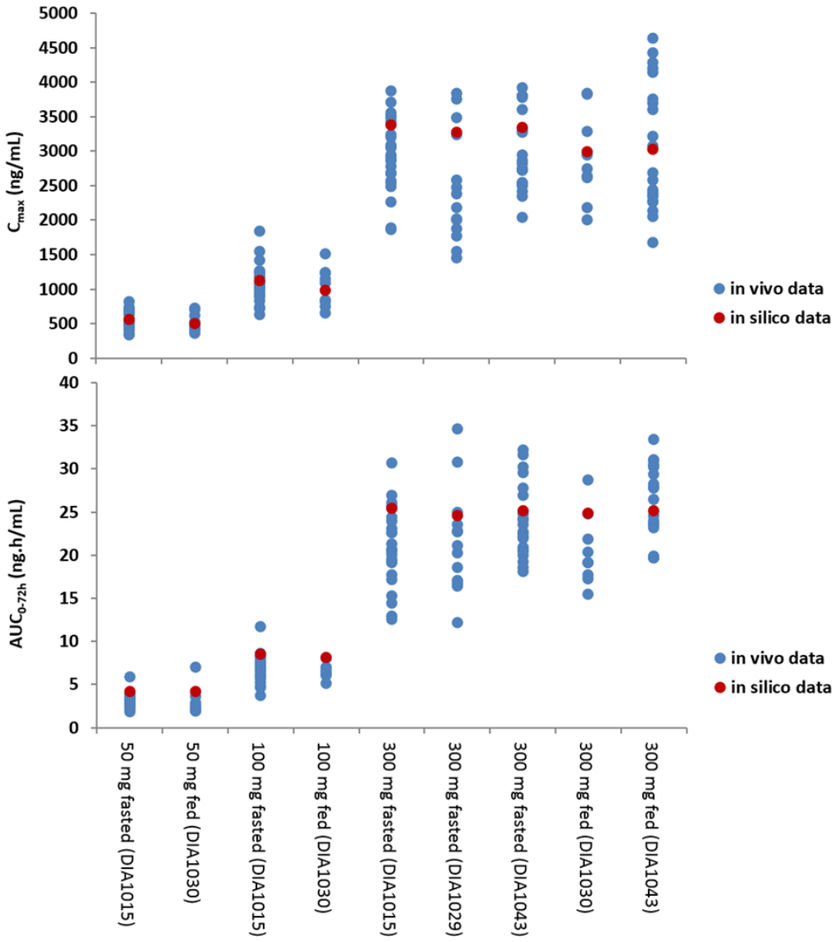
VBE – Virtual Bioequivalence – Example 2

Steps taken in model building

- Physiochemical characteristics of both APIs compared (in vitro)
- Model Development (using registered crystal form)
  - Phys chem properties
  - In vitro biopharmaceutical expts
  - Biorelevant dissolution
  - Verified using clinical PK data at various doses in fasted and fed conditions and a range of API PSDs
- In silico risk assessment of new crystal form using the above PBBM model and the biopharmaceutical properties of the new form

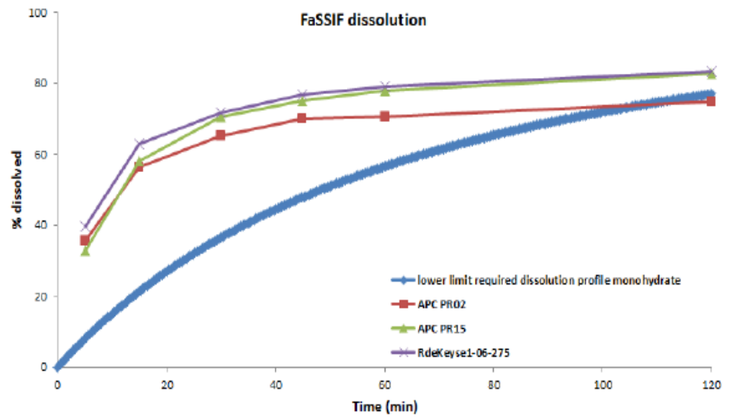
VBE – Virtual Bioequivalence – Example 2

Model verification & VBE out come



Fasted- In silico	Geometric Mean		
	Polymorph 2	Polymorph 1	GMR (90% CI)
C_{max} (ng/ml)	3256	3408	95.5 (88.3-103.4)
AUC $_{0-72h}$ (ng.h/ml)	26248	26239	96.4 (92.4-100.5)

Fed- In silico	Geometric Mean		
	Polymorph 2	Polymorph 1	GMR (90% CI)
C_{max} (ng/ml)	2798	3167	88.4 (80.9-96.5)
AUC $_{0-72h}$ (ng.h/ml)	25217	27358	92.2 (89.0-95.4)



- VBE simulations did not indicate any changes in the oral bioavailability when comparing both forms.
- A negative effect on the oral bioavailability and absorption rate would require a significantly slower physiology based in vitro dissolution
- Confirmatory clinical study was performed testing 10,50 and 90% of the new form
- All formulations are BE confirming the in silico assessment

VBE – Virtual Bioequivalence

Points to Consider

- Number of datasets available to verify/validate the initial model
- Appropriate population size for VBE (n=12, 24, 48 or based on clinical studies?)
- Number of studies to simulate (n=10, 50, 200?)
- Inclusion of inter and intra variability
  - Variability on C_{max} and AUC
  - Propagate intrasubject variability mechanistically (bottom up)
- When can VBE help in a program?
  - Timing in the program
  - Scientific (internal) or regulatory Q
  - If regulatory
    - timing of interaction
    - detail available
    - learn & confirm
    - global alignment

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