EUROPEAN MEDICINES AGENCY
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EMA expectations in building a safe space based on PBBM

M-CERSI Workshop
Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

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Outline

- Background
- Case 1: PBPK modelling – clinically relevant specifications
- Case 2: Level A IVIVC manufacturing changes
- Learnings

What are we looking for?

The ultimate goal is to assure consistent *in vivo* product performance (safety and efficacy) for the marketed product relative to the clinical trial formulation.

The role of specifications is to guarantee that products meet clinical performance and that processes are performing as expected.

What are we looking for? How?

Traditionally specifications driven by regulatory and compendial expectations, aiming primarily at quality control and ensuring batch-to-batch consistency.

Mainly based on evaluation of developmental, process validation and failure batches.

What are we looking for? How?

- Applying QbD principles

⬇

- Better process and product understanding

⬇

- Higher assurance of product quality

⬇

- Consistent ***in vivo* performance**

(safety and efficacy profiles)

<u>marketed product relative to the clinical trial formulation</u>

Product ***quality***

Process ***robustness***

⬇

This order cannot be reversed

⬇

Consistent ***in vivo* performance**

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Case 1: PBPK modelling-clinically relevant specifications

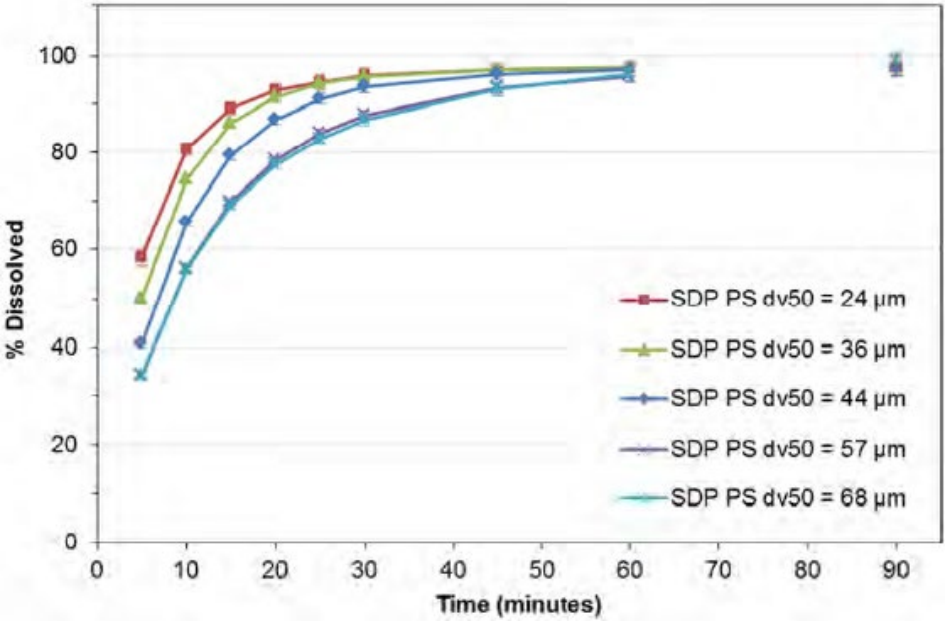
BCS 2 compound (low solubility, high permeability)

spray dried powder (SDP)

SDP is a solid dispersion of the API in a HPMC polymer,

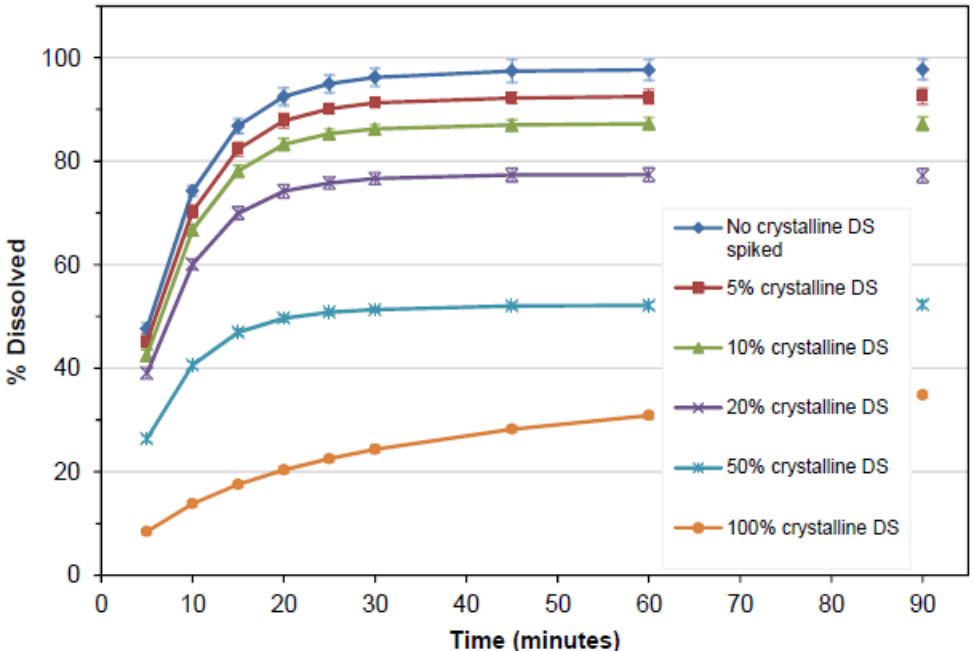
Single strength immediate release, film-coated tablet

Case 1: PBPK modelling-clinically relevant specifications



Effect of spray dried powder (SPD) particle size distribution

Effect of active substance crystallinity



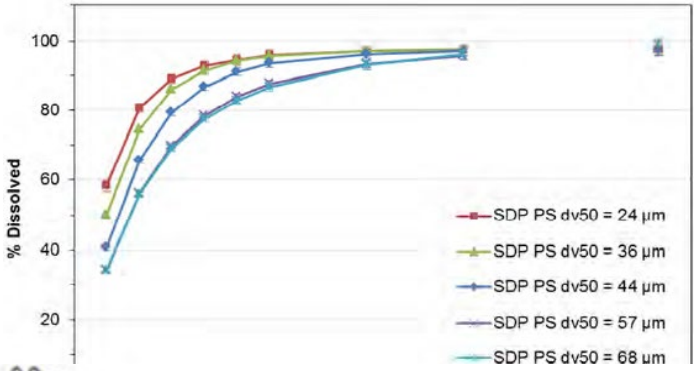
Case 1: PBPK modelling-clinically relevant specifications

#1. Is the mechanistic absorption model:

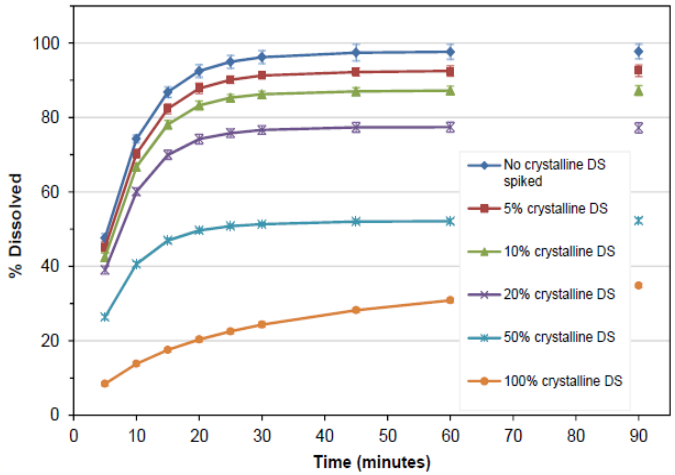
a) adquate? suitable?

b) predictive (for in vivo performance) of formulation

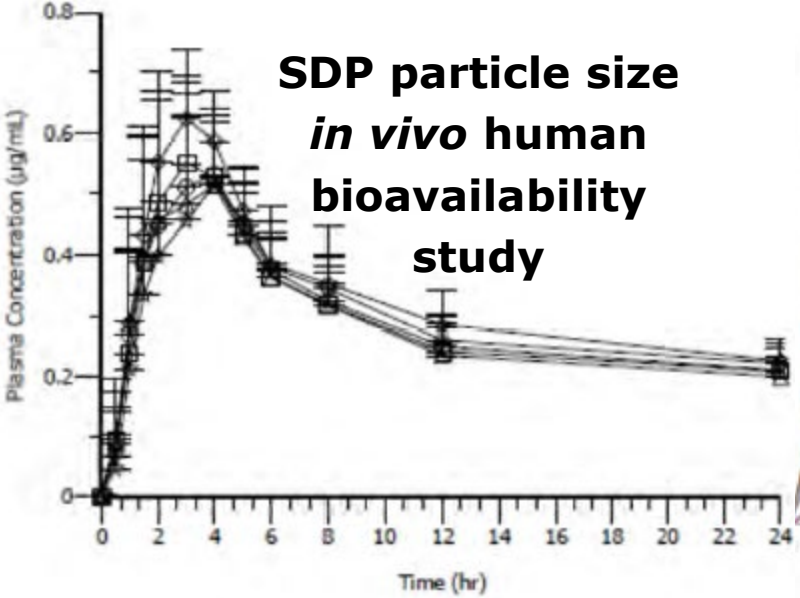
Case 1: PBPK modelling-clinically relevant specifications



presence of **crystalline substance mechanistic absorption modelling and virtual bioequivalence study**



SDP particle size *in vivo* human bioavailability study



Case 1: PBPK modelling-clinically relevant specifications

Assessment **conclusions/recommendations**

- The absorption components are well developed.
- The **discussion around the input parameters** (e.g. the source of Log P, pKa permeability) **and their uncertainty**, is considered **insufficient.**
- **Model verification** and ***in silico*** predictions of the crystals effect are **insufficient**; **not supported** by data **in humans,** thus it is **informative**, but not **definitive**.
- **Prediction error** values are within a **10% to 30%,** considered **too wide.**
- The **clinical relevance** of any **mis-prediction** should always be **discussed.**
- **Intended purpose** of the model is **not clear**; Specifications not proposed

Case 1: PBPK modelling-clinically relevant specifications

#2

Can a mechanistic modelling approach be used to justify the setting of clinically relevant drug product specifications for other critical quality attributes such as solid state crystallinity?

Case 1: PBPK modelling-clinically relevant specifications

- Any critical quality attribute that might be clinically relevant could be evaluated in the mechanistic PBPK model.
- But the model **should be shown to be predictive** of the ***in vivo*** performance observed.
- Once the model has been adequately qualified, it is agreed that it could be used to determine the level of crystallinity considered clinically relevant (BE threshold).
- **BUT** specifications should also guarantee an adequate manufacturing control (i.e. batch to batch consistency).

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- Case 2: Level A IVIVC - manufacturing changes
- Learnings

Case 2 – Level A IVIVC manufacturing changes

- ✓ BCS class II, film-coated, modified-release (MR) tablet at 3 strengths.
- ✓ All 3 strengths qualitatively the same; same release mechanism.
- ✓ Three formulations (slow, target, fast) were studied and showed distinct *in vitro* dissolution profiles.
- ✓ *In vivo* PK data were deconvoluted into *in vivo* dissolution profiles. The rank order was maintained in the deconvoluted *in vivo* dissolution profiles as in the *in vitro* profiles.
- ✓ Level A IVIVC was developed for the *in vivo* and *in vitro* dissolution profiles. using the Phase III MR highest strength tablet for the three MR formulations.
- ✓ *Scope:* To allow future changes in formulation / move of production site(s).

Case 2 – Level A IVIVC - manufacturing changes

- ✓ Internal predictability was evaluated using commercial software to convolute plasma concentration-time profiles for the three MR formulations using the developed Level A IVIVC.
- ✓ Robustness of the Level A IVIVC, was performed by cross validation by developing a Level A IVIVC with only two formulations, testing internal predictability with the two formulations, and testing external predictability with the third formulation.

Case 2 – Level A IVIVC - manufacturing changes

#1

Is the Level A IVIVC appropriately developed for the intended use?

Case 2 – Level A IVIVC - development

Assessment conclusions/recommendations

MR developed to prevent high plasma concentrations. Hence, Cmax should be predicted accurately by the level A IVIVC.

A solution was used as reference product for the IVIVC and the three MR formulations which were not bioequivalent for Cmax. Reference and MR formulations are adequate for development of an IVIVC.

The PBPK modelling included individual variability in the model.

Weibull parameters used to describe the *in vitro* dissolution profiles, instead of observed *in vitro* data; **this should be discussed and justified.**

Time scaling applied in line with a single relationship for the three MR formulations.

Case 2 – Level A IVIVC - development
Assessment conclusions/recommendations

Internal predictability was used to evaluate the IVIVC and to test the robustness of the Level A IVIVC, cross validation was performed by developing a Level A IVIVC with only two formulations, testing internal predictability with the two formulations, and testing external predictability with the third formulation.

This approach may be considered acceptable as minimal validation but it should be noted that the slow MR formulation was outside the acceptance predictability.

Therefore, the **robustness and applicability** of the IVIVC should be **demonstrated** with **several pilot and clinical phase 3 batches** especially since **the robustness** of the dissolution test has **not** been **demonstrated**.

Case 2 – Level A IVIVC - development

Assessment conclusions/recommendations

In this IVIVC the modified release polymer has been varied between the three formulations.

The Applicant not only plans to use the level A IVIVC to support changes from manufacturing sites but also other very small quantitative composition changes. These changes are considered possible to affect the dissolution of the formulation.

Hence, the **dissolution profiles** of batches used in **phase 3 studies** should be compared with those with **newly proposed quantitative composition changes** (see next slides).

Case 2 – Level A IVIVC - manufacturing changes

Proposal to establish equivalence between the high strength product manufactured at different facilities, by using the Level A IVIVC *in vitro* dissolution test and f2 statistical parameter as similarity factor.

Proposal to carry out no comparative dissolution on the 2 other lower dose strengths as IVIVC developed covers the 3 dose strengths.

#2

I*s the Level A IVIVC appropriate for the intended use?*

Case 2 – Level A IVIVC - manufacturing changes

Assessment conclusions/recommendations

The use of the Level A IVIVC in vitro dissolution test to demonstrate the equivalence between the product manufactured at 2 facilities might be acceptable provided that the points raised regarding the establishment of IVIVC are met.

- The number of (pilot/biobatch/commercial scale) batches to be used to ensure equivalence between the drug products manufactured at different sites should be discussed; at least three batches per site to be included
- how inter- and intra-batch dissolution variability are addressed.

Case 2 – Level A IVIVC - manufacturing changes

Assessment conclusions/recommendations

The proposed ***f2 statistical parameter*** as similarity factor is not agreed.

Based on the IVIVC data, virtual trial simulations with "virtual formulations" and the therapeutic window of lower and upper dissolution limits will be set. It is envisioned that these **limits will be stricter than the 10% for f2 similarity** statistics given the rather small differences in dissolution for the three MR formulations while these formulations were not bioequivalent.

Case 2 – Level A IVIVC - manufacturing changes Assessment conclusions/recommendations

NOT carrying out comparative dissolution on the 2 other dose strengths not agreed; tablets are not dose proportional neither comply with the 5% rule (Guideline on bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1)).

The results of the IVIVC for the high strength formulation can be extrapolated to the other strengths, by means of **pharmacokinetic dose proportionality following single dose and multiple dose** (Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) and **by comparative dissolution tests of the three strengths**.

The therapeutic window should also be considered in the acceptability of the IVIVC (some indication in the data of a small therapeutic window).

Case 2 – Level A IVIVC - manufacturing changes

#3. in vitro dissolution method acceptability for the IVIVC?

Data

Dissolution method development for IVIVC was conducted with both USP 1 (basket) and USP 2 (paddle) apparatus in various pH of media and different agitation/rotation speeds. The medium and agitation speed were selected as they showed to be the optimized conditions.

The *in vitro* dissolution method was found to demonstrate sufficient discrimination.

Case 2 – Level A IVIVC - manufacturing changes Assessment conclusions/recommendations

The selected dissolution medium, volume of the medium and agitation speed (also in other media) should be justified.

The selected time points should be presented and justified; should sufficient to fully characterise the profile, incl. the plateau.

The results of different dissolution tests/conditions should be presented to allow identification of the dissolution tests that provides the most suitable discrimination.

Development of the in vitro dissolution method should be presented in detail to allow assessment of the suitability of method for the purpose of IVIVC.

outline

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Learnings 1/3

- Any critical quality attribute that might be clinically relevant could be evaluated in the (mechanistic PBPK) model.
- Specifications should also guarantee an adequate manufacturing control.
- An established Level A IVIVC may be used to support changes from manufacturing sites without the need to conduct bioequivalence studies.

Learnings 2/3

Model:

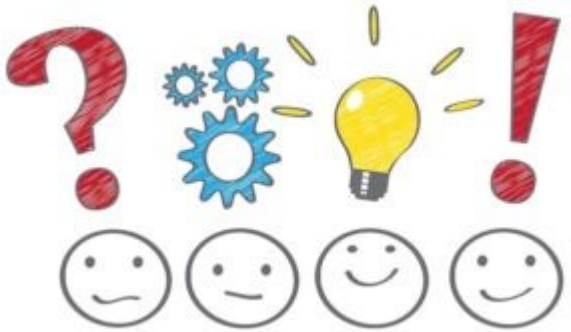
- **Describe sufficiently:**
  - The mechanistic absorption model
  - Intended purpose of the model
  - The development of the *in vitro* dissolution method to allow assessment of the suitability of method for the purpose of use.
- **Discuss in detail:**
  - Model input parameters and their uncertainty,
  - Model verification (data in humans),
  - Prediction error – see IVIVC.
  - Any mis-prediction

Learnings 3/3

- The general approach should be in line with the recommendations for a level A IVIVC described in appendix III of Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) and Guideline on quality of oral modified release products (EMA/CHMP/QWP/428693/2013).
- NTI drugs are not precluded from IVIVC modelling; if the therapeutic index would ultimately be considered narrow a tighter 90%CI for the IVIVC model could be agreed on
- **Multidisciplinary: MSWG - PKWP - QWP**

Thank you for your attention

Questions?



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