Hybrid as registration route for alternative formulations and posologies to increase patient comfort/adherence

22 September, 2023

Proud to be the Highest Ranked CRO in the World
at the 2022 CRO Leadership Awards

Introduction

- Application in accordance with paragraph 3 of Article 10 ("hybrid“ medicinal product)
  - Refer to a European reference product, requires a bridging approach
  - Applications rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data
  - THIS IS NOT A ROUTE FOR FAILED GENERICS
  - *extent of the additional studies required depends on what is proposed and will be a matter of scientific assessment by the relevant competent authority.*
    - Implies discussions, integrating different points of view within sponsor teams and between assessors from the authorities

Introduction

Examples in Notice to Applicants

		Additional data usually required
a)	different salt/ester complex/derivative (with the same therapeutic moiety)	Evidence that there is no change in the pharmacokinetics of the moiety, pharmacodynamics and/or in toxicity which could significantly change the safety/efficacy profile (otherwise, to be considered as a new active substance)
b)	different route/pharmaceutical form (For parenteral administration, it is necessary to distinguish between intraarterial, intravenous, intramuscular, subcutaneous and other routes) i) new route of administration ii) new pharmaceutical form (same route) (conventional to modified)	Clinical data (safety/efficacy), pharmacokinetics, pre-clinical (e.g. local toxicology), if justified
c)	different strength same route/ pharmaceutical form and posology	Bioavailability (cf. guideline)
d)	suprabioavailable products i) same dosage intervals but reduced doses intended to achieve same plasma/blood concentrations as a function of time	Bioavailability studies may suffice (see paragraph 5 of Bioequivalence guideline).
e)	active substances associated in a different proportion/different posology or if one or more is intended for modified release.	Clinical studies comparing existing/new proportion or dosage regimen, including bioavailability studies.

Points to consider

- changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration compared to the reference product
  - What can be impacted by these changes? Safety? Efficacy? Both?
  - What can be done to demonstrate the claims of the proposed product?
- Reference can be made to the dossier of a reference medicinal product for which a marketing authorisation has been granted in the Union in accordance with Articles 8(3), 10a (WEU), 10b (FDC) or 10c (informed consent) of Directive 2001/83/EC.
- If the sponsor is the global MA holder, may consider a line extensión

Examples: Immediate release

- Low soluble drug substance in the market in a large dosage form and high dose due to limited bioavailability
  - Patients have swallowing difficulties and variability in exposure due to limited BA
  - Propose change in strength and supravailable product
    - for example, solid dispersion or formulation that has higher bioavailability. Dose (API content) is reduced but target same exposure as marketed product
  - Bioequivalence only? Fasting and fed? Interactions (e.g. proton pump inhibitors)?
  - Can differences in toxicity and effect be excluded?

Examples: Immediate release

- Strengths available in the market need to be scored/divided to adjust posology to patient response or needs
  - Propose a new strength within the approved posology dose range
  - Is PK linear? Is dose response steep enough to justify intermediate dose?
  - Bioequivalence compared to approved higher strength (e.g. 2x new strength versus approved) or versus half tablets (same dose)?
- Pediatric appropriate formulations
  - What is the strategy for pediatric dose definition? Extrapolation from adult PK?
  - Can comparative bioavailability in adults or bioequivalence be sufficient?

Example: Modified release

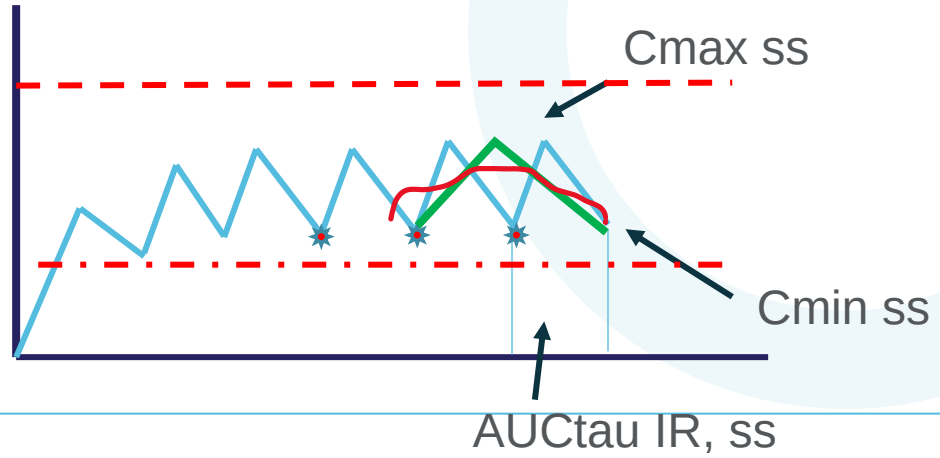
- Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms
  - Application for a modified release formulation of a drug that is authorized in a formulation with a different release rate
  - PK data alone may not be sufficient for evaluating whether the benefit/risk ratio of the modified release formulation is comparable to the corresponding doses of the immediate release form
    - European context expects superiority or non-inferiority to marketed product
    - Note FDA context expects efficacy versus placebo
    - The new formulation should be characterized in appropriate single dose and multiple dose pharmacokinetic, pharmacodynamic and clinical efficacy/safety studies
    - As a principle, comparative efficacy and safety is required, unless adequately justified…

Example: Modified release

- Requires bridging to the reference product
  - Similar total systemic exposure to waive toxicology, pharmacology and clinical tests related to active substance
- What can be different?
  - Can the metabolic profile be different? Determine metabolites
  - Local tolerability? Animal studies? Healthy volunteers? Patients?
- Are you targeting the same indication?
  - If not, is the mechanism of action the same, can you extrapolate?
  - Acute or maintenance treatment?
  - Population?
    - Patients stable on a therapy or initiation therapy?
    - Adults, children, elderly, special populations?

Example: Modified Release

- Is there a well established concentration effect relationship?
  - Can assess modified release versus immediate release using PK/PD studies
  - Waive studies based on PK
    - Same daily profile shape allows to claim bioequivalence
    - Bioequivalence in max, min and exposure with different profile shape
    - Same exposure and max and min within therapeutic window



Same exposure claims based on:
AUCtau XR,ss=2xAUCtau IR,ss

Example: Modified Release

- Some “details”:
  - Must address if change in profile shape can influence PK/PD relationship
  - Must justify appropriateness of established PK/PD model. Is it fit for purpose?
    - Can you simulate complete time course of effect?
    - Is the variability in parameter estimates appropriate for comparison of effect in cases of similar exposures?
    - Would you use the PK/PD model to justify a different posology in a subpopulation?
  - Simulations: focus on clinical trial scenarios.
    - Ideally, PD endpoint simulated is in line with indication guidelines and is established as linked to clinical outcomes

Example: Modified Release

Comments on potential impact of shape

$continuous\ PD\ endpoint\ = \frac{Emax \times Cp}{EC50xCp}$	PD in time can be simulated from PK in time. How can a change in shape change the fn?

Event rate PD = endpoint	Fn (baseline rate; placebo response, exposure metric)	Response rate can be linked to exposure metric (e.g. AUC, Cavg). How can a change in profile shape change the fn?

Are products with different profile shapes included in the PK/PD model building (e.g. QD vs BID)?
Is the PD endpoint relevant for the claim of the XR?

Example: Modified Release

- Therapeutic studies
  - assess the intensity and duration of the therapeutic effect and undesirable effects of the modified release formulation in comparison with the authorised immediate release formulation.
  - May need to generate information on onset of effect and/or maintenance of effect towards the end of the dosing interval
  - If safety and efficacy is closely related may need to show therapeutic equivalence
  - May require inclusion of a placebo arm to ensure study sensitivity
  - Take into account therapeutic study guidelines for the indications
    - May simplify or not depending on the claim pursued (e.g. reduced risk of relapse)
  - Can the primary endpoint be a PD metric? Is it related to clinical outcome?

Closing remarks

- Case-by-case approach
- Plan in several scientific advice rounds
- Relevant questions will be brought up during MAA assessment due to different ways to look at the issue
  - Formulation
  - PK
  - PK/PD
  - Clinical Efficacy and Safety
  - Medication errors
  - What does this hybrid product add to the therapeutic armamentarium?