EMA/EGA JOINT WORKSHOP ON THE IMPACT OF THE REVISED EMA GUIDELINE ON MODIFIED RELEASE DOSAGE FORMS
www.egagenerics.com
LONDON
30 April 2015
European Medicines Agency

Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)

Injectable modified release products

Dr Sotiris Michaleas,

National Expert for the Greek National Organization for Medicines
Assistant Professor Pharmacy

European University, Cyprus

Disclaimer

This presentation represents the author's personal views and does not necessarily represents the policy or recommendations of the National Organization for Medicines or EMA

Outline of this presentation

- Injectable MR products of NCEs (Section 4 Subsection 4.3)
- Injectable MR products of drugs authorized in a formulation with a different release rate
- Injectable MR formulations under abridged applications referring to marketed MR products

Definitions

- Intramuscular/subcutaneous depot formulations: A depot injection is usually a SC or IM product which releases its active compound continuously over a certain period of time.
  - in vivo delivery is designed to continue for 1-2 months.
- Subcutaneous depot formulations include implants.

Injectable MR formulation of NCEs

- It is a full dossier
- Complete Pharmaceutical and chemical data required
- Necessary preclinical studies
- Complete clinical data package

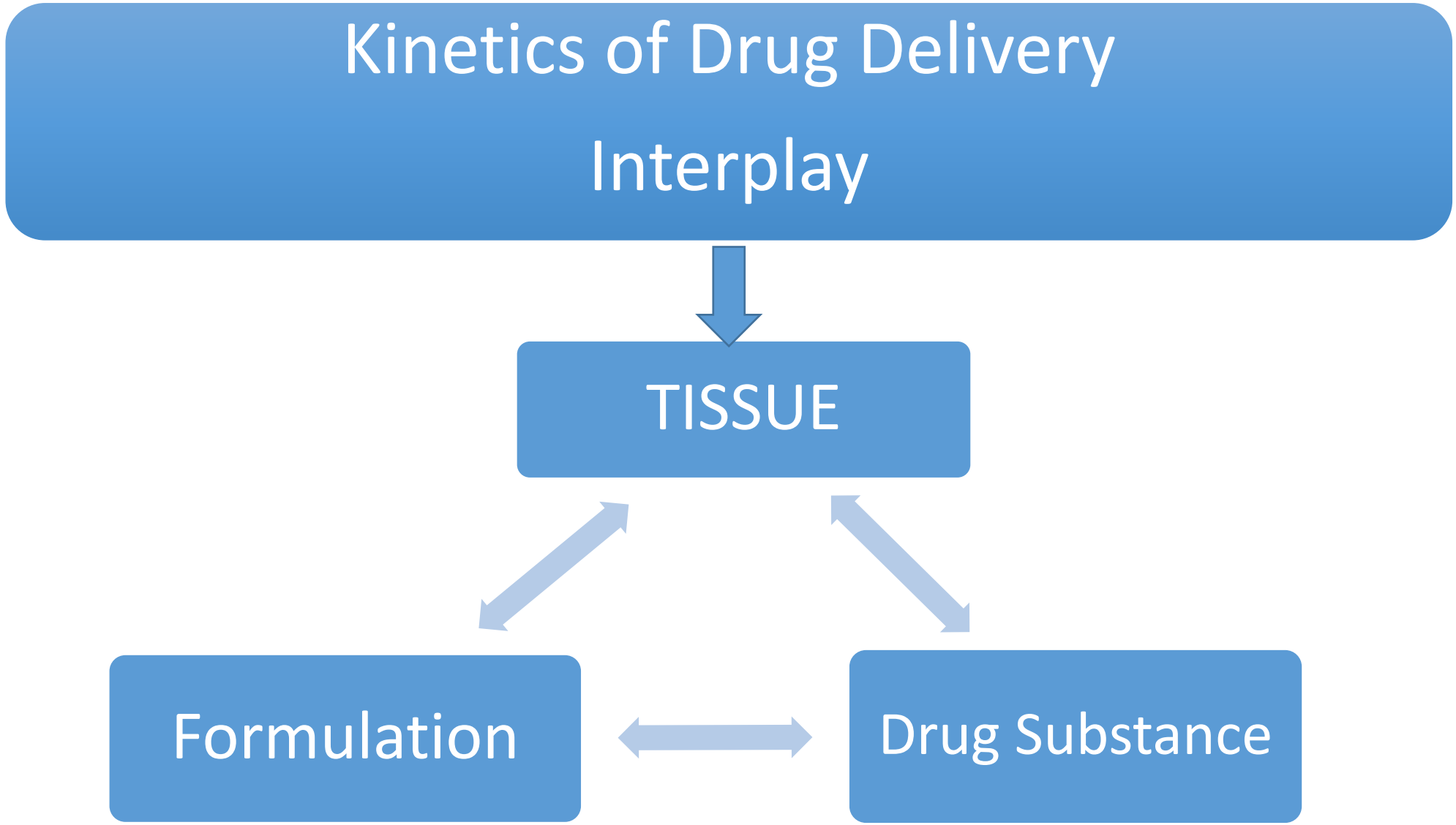
Guidance is provided for the PK studies required
Common with section 5.1

ADVICE

"PK studies with the MR formulation should be initiated **as early as possible** during clinical development"

To avoid duplication

PK studies for injectable formulations of NCEs



PK Studies for injectable formulations of NCEs

In vitro and in vivo studies to evaluate:

- Drug diffusion characteristics
- Rate limiting step for systemic availability
  - e.g. drug release

PK Studies for injectable formulations of NCEs

PK studies:

Single dose &

Multiple dose

- Application site dependent absorption
- Fluctuation
- Lag times
- IVIVC is advisable
- Dose proportionality in case of several strengths

Injectable MR formulation of a drug that is authorized in a formulation with a different release rate

General Assumptions of the section

- Similar total systemic exposure of active substance/metabolite
- Active substance intrinsic properties well-known Investigation not required

General Considerations

- Rationale to develop MR:
  - A relationship between the pharmacological/toxicological response and the characteristics of systemic exposure to the active substance/metabolite(s) exists
- The aim of the MR formulation:
  - to reach a similar total exposure (AUC) to active substance as for the immediate release formulation.
- Keep in mind:
  - the MR formulation is not bioequivalent to their IR form
  - the MR formulation may have a different extent of absorption or metabolism i.e. different nominal doses are given
  - PK data alone may not be sufficient
  - additional efficacy/safety data will generally be required
  - Waiving of therapeutic studies possible

Overview of studies

- PK/PD studies
  - Single dose studies
  - Multiple dose studies (in case of accumulation)
- Clinical Efficacy and Safety studies (may be waived)
- Additional studies may be required:
  - Characterization of metabolic profile if a different route of administration
- Reference Product: the marketed IR product of the same active substance
- Test Product: the final formulation to be marketed. Any differences should be shown not to affect
  - Release characteristics
  - Bioavailability

PK parameters to be investigated

- the rate and extent of absorption
- fluctuations in drug concentrations **at steady state**
- **inter-subject** variability in PK arising from the drug formulation
- dose proportionality
- factors affecting the performance of the MR formulation
- the risk of unexpected release characteristics (e.g. dose dumping)

Study design Issues

- concentration measurements of the active substance and/or metabolite(s)
- **Active Metabolites are required**: changes in route or absorption rate may modify extent and pattern of metabolism
- **Subjects**: Healthy volunteers or patients if safety issues exist
- Steady state for multiple dose studies **should be confirmed**
- Multiple dose studies can be waived in case of **no accumulation**

Multiple dose studies: New Key concepts

- **No Accumulation**: Possible to waive MD studies
  - Insignificant levels at the end of the dosing interval
  - A single dose study at the highest strength has shown that:
    - mean$AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-oo)}$
    - For both test and reference
- **Achievement of steady state**
  - Comparison of at least three pre-dose concentrations
  - For each formulation
  - Apparent half life to be taken into account
- **Direct switching** between treatments (overlap of washout and build-up phases)
  - Sufficiently build-up period is required
  - At least 5 times the terminal half life

Rate and extent of absorption, fluctuation

- PK parameters for single dose studies
  - AUC(0-t), AUC(0-∞), residual area,
  - Cmax , tmax, t1/2 and tlag
- PK parameters for multiple dose studies
  - AUC(0-τ),
  - tmax,ss, Cmax,ss, Cmin,ss
  - fluctuation.
- Support of the claimed release characteristics
  - Calculate cumulative amount absorbed
  - Determine rate of absorption versus time
- Fluctuation of the MR product similar or less than the IR product.
- Dose levels and strengths to be evaluated:
  - linear PK: one dose level (SD only or SD and MD if accumulation exists)
  - Non linear PK: highest and lowest strength (when extent of non linearity similar for IR and MR)

Variability

- The inter-individual variability of the PK parameters should be determined
- The variability for MR formulation should preferably not exceed that for the IR formulation, unless justified for potential clinical consequences.

Dose proportionality for several strengths

- dose proportionality for different strengths / doses of the MR formulation should be adequately addressed.
- PK parameters of interest of all the strengths/doses are compared after dose adjustment.
- **not applicable:** The criteria described in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) for dose proportionality based on AUC only and 25% acceptance range as these criteria only apply for strength selection for BE studies.

Unexpected release characteristics

- **dose dumping**: rapid drug release of the entire amount or a significant fraction of the active substance
- deficiency of the biopharmaceutical quality
- **significant risk** to patients, either due to **safety** issues or diminished efficacy or both
- Should be studied and excluded for depot formulations

Influence of site of application on plasma levels

- Important for SC/IM depot and TDDS formulations when **application site is not limited to one body area**
- Safety and tolerability at the site of application should also be assessed
- it should be investigated
  - that the plasma levels are within the therapeutic concentrations at the end of the dosing interval
  - how the plasma levels decrease after removal of the depot formulation.

Therapeutic studies

- demonstrate that the new MR formulation **is as safe and effective as the existing formulation.**
- **Additional benefits** of the new formulation should be shown or justified, if claimed
- Studies can be waived in certain cases

Waiving of therapeutic studies

- **CASE A** the new MR product is developed to actually mimic the performance of a product with a different release mechanism and its dosage regimen
  - BE shown in terms of Cmax,ss, Cmin,ss and AUC(0-τ)ss e.g. a pulsatile multiphasic release dosage form.
- **CASE B** differences in the shape of the plasma concentration-time profile are shown to have no relevance for efficacy and safety based on the exposure – response and profile shape - response relationships.
  - BE is shown in terms of Cmax,ss, Cmin,ss and AUC(0-τ)ss

Waiving of therapeutic studies

- **CASE C** there is **a well-defined therapeutic window** in terms of safety and efficacy:
  - the rate of input is known not to influence the safety and efficacy profile or the risk for tolerance development and
  - BE is shown in terms of AUC(0- τ),ss and
    - Therapeutic window of the test is enclosed in that of the reference
    - Cmax,ss test≤Cmax,ss reference
    - Cmin,ss test ≥Cmin,ss reference.

Clinical studies: Design Aspects

- compare the intensity and duration of the therapeutic effect and undesirable effects
- establish any claims of clinical benefit of the new formulation
- Efficacy assessment: Quantify pharmacodynamic or clinical effects of the concerned therapeutic class
- In exceptional cases only: extrapolation to indications other than those investigated in the trial
- safety studies may be required when the prolonged therapeutic activity may alter the safety profile of the drug

Clinical studies: Design Aspects

- **non-inferiority** of therapeutic efficacy or **equivalence**: comparison is made on the basis of equal exposure (ICH E9 recommendations)
  - In case efficacy and safety are closely related **equivalence studies are needed**
  - **non-inferiority studies** might be sufficient if safety established
- The type of studies that are required depends on whether
  - appropriate, pharmacodynamic endpoints can be defined,
  - the relationship between the pharmacodynamic markers and clinical efficacy is known,
  - assay sensitivity is guaranteed
  - a non-inferiority margin or equivalence margin can be defined.
- A **placebo arm or an additional active arm** with a lower dose is mandatory if assay sensitivity of the trial cannot be guaranteed (see ICH E10).
- equivalence or non-inferiority margins have to be defined and justified

Clinical studies: Design Aspects

- **New Indication**: A clinical development plan in accordance with existing guidelines or the state of the art is required
- **Local safety** should also be addressed.
- The **remaining amount of active substance** after depot formulation removal should be considered in respect to safety concerns due to potential misuse or environmental risks.
- **Superiority claim** has to be proven with clinical trials.
  - refer to the scientific guidance documents relevant to the concerned therapeutic area.
- If a claim is made for **fewer systemic adverse reactions** for the modified release form, this has to be substantiated.

Abridged applications for MR forms referring to a marketed MR form

Studies to demonstrate BE

- a single-dose study comparing test and reference products
- a multiple-dose study comparing test and reference product **in case of accumulation.**

Selection of strengths to be evaluated

- Only one strength has to be investigated if the different strengths are
  - proportional in composition
  - exhibit a similar in vitro dissolution profile.
- The strength should be selected based on the PK linearity and safety.
- A **bracketing approach** is possible for several non-proportional strengths
  - the formulation strategy of the reference product should be taken into account.
- When the originator product is marketed in only one concentration and the different doses are achieved by choosing the total volume to be injected:
  - in case the reference is dose proportional **any dose is acceptable for a BE trial**

Safety Issues with IM/SC depot formulations in healthy volunteers

- non-therapeutic doses to healthy volunteers may be acceptable
- multiple dose studies in patients are also acceptable to show bioequivalence

Appendix 1. IVIVC
Concepts regarding in vitro in vivo correlation for novel injectable depot formulations

In vitro in vivo Correlation IVIVC

Definition

An in vitro in vivo correlation (IVIVC) is a mathematical model describing the relationship between an in vitro property of a dosage form and a relevant in vivo response.

dissolution or drug release **vs** **drug plasma concentration or amount absorbed**

Concepts regarding in vitro in vivo correlation for injectable depot formulations

- Highly recommended for injectable depot formulations
  - to quantify in vivo release and formulation related effect on absorption,
  - to establish the in vivo relevance of in vitro dissolution tests and associated dissolution specifications
  - to support biowaiver claims in later phases of clinical development or post-authorization if there are changes in formulation.
- Different levels A, B, C
- Level A IVIVCs, in contrast to levels B and C, predict the entire concentration-time profile and for this reason are highly encouraged.
- The more accurate the IVIVC model the more useful

Concepts regarding in vitro in vivo correlation for injectable depot formulations

Reference formulation for deconvolution RFD

- Two MR formulations with different dissolution profiles are compared versus a fast releasing formulation in a crossover study.
- Estimation of the in vivo release of drug as a function of time for each MR formulation
- For intramuscular/subcutaneous depot formulations, an appropriate RFD would be an aqueous solution administered by the same route (preferable) or an IV formulation.

Sampling Times

Sampling Times

- for injectable controlled release formulations, in vitro release testing is often designed to be complete within 24-48 h
- the in vivo delivery is designed to continue for 1-2 months.
- a time-scaling factor or a range of factors built into the model to account for uncertainty in expected in vivo release
- to provide a more realistic picture of the expected in vivo behavior and better choice for appropriate sampling times for the test formulations.

In conclusion

- More detailed guidance on investigation o PK parameters is provided
- Multiple dose studies still required but can be waived if no accumulation
- Therapeutic studies can be waived in certain cases
- IVIVC is highly recommended
- Non therapeutic doses to healthy volunteers may be acceptable
- Multiple dose studies to patients may replace single dose studies to healthy volunteers for safety/ethical reasons

Thank you for your attention