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Concepts and Strategies in Drug Development

MR products as line extension of already approved IR forms

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Outline of presentation

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Development rationale/goals

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General statement/concept

Modified release forms are developed based on the rationale that there is a relationship between the pharmacological/toxicological response and the characteristics of systemic exposure to the active substance/metabolite(s). The aim of the modified release formulation is therefore, in most cases, to reach a similar total exposure (AUC) to active substance as for the immediate release formulation. This does not necessitate that the same nominal doses are given (the modified release formulation may have a different extent of absorption or metabolism).

Consequences for assessment of systemic exposure

- expectations (comparison with existing IR form)
  - "similar" total exposure: "same"/"(bio)equivalent"? "comparable"?
- development conditions/degrees of "freedom"
  - nominal dose may be higher (label claim) ...
  - ... certain loss in exposure may be acceptable for MR form
  - ⇨ however: higher risk of "dose dumping"?

PK/clinical consequences

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General statement/concept

In general modified-release formulations are not bioequivalent to their immediate release form. Consequently 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. Therefore additional clinical data will generally be required, unless otherwise justified

Assessing BA/BE: study goals

- development rationale (product with significantly different release characteristics) ...
- ... excludes bioequivalence
- consequences:
  - *"PK data alone may not be sufficient"*
  - but: are there cases where PK profiling is appropriate/sufficient?
  - *"additional clinical data generally required, unless otherwise justified"*
  - circumstances where clinical studies may be avoided?

Specific requirements

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CHMP Guideline

- general expectation
  "The applicant has to prove that the benefits of the new formulation overweight potential risks (medication error) ..."
- suggested studies (reference: approved IR preparation)
  - appropriate single and multiple dose PK studies ...
  - ... pharmacodynamic and clinical efficacy/safety studies
  - additional PK studies may be needed on metabolic profile (e.g. in cases of new route of administration)
- investigations not considered necessary
  - toxicological/pharmacological/clinical studies characterising intrinsic properties of the active drug ingredient ...
  - ... assuming "similar" total exposure of the active moiety (IR *vs.* MR)

Pharmacokinetic studies

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Purpose: *in-vivo* characterization product performance

- rate and extent of absorption (comparison with IR product)
- fluctuation at steady state (comparison with IR product)
- inter-subject variability in PK arising from the formulation (comparison with IR product)
- dose proportionality
- factors affecting performance of MR product
- risk of unexpected release characteristics ("dose dumping")

Specific conditions (deviating from BE assessment)

- necessity to measure active metabolites
  - conditions described in BE Guideline (2010) not applicable ...
  - ... considering impact of modified absorption rate on metabolic pattern

Multiple dose studies

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Requirement(s)

- studies generally needed ...
- ... except in cases of "no accumulation"

Administration conditions according SmPC of IR form

- steady state built-up
  - "fasted state" or "irrespective of food"
  - specific timing related to food intake suggested ...
  - ... conditions should be adjusted accordingly throughout the study
- profiling day(s)
  - "worst case fasted conditions" (overnight fast until 4 h postdose) ...
  - ... timing related to food intake as recommended
- recommended intake under fed conditions ...
  ... composition of food should be "normo-caloric"

Absorption, fluctuation

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Rate and extent of absorption

- conventional PK characteristics
  - single dose: AUC_{0-t}, $AUC_{0-\infty}$, residual area, C_{max}, t_{max}, $t_{1/2}$, t_{lag}
  - multiple dose: $AUC_{0-\tau}$, $t_{max,ss}$, $C_{max,ss}$, $C_{min,ss}$, fluctuation
- primary parameter to be defined to reflect efficacy/safety
- claimed release characteristics should be demonstrated
  - suggested procedure: deconvolution technique (comparison with IR) ...
  - ... cumulated amount absorbed & rate of absorption *vs.* time

Fluctuation at steady state

- well-established characteristics: Peak-Trough-Fluctuation
- expectation: PTF of MR similar or less than IR product ...
- ... seems not adequate in all cases, e.g. QD (MR) vs. TID (IR)

Absorption, fluctuation

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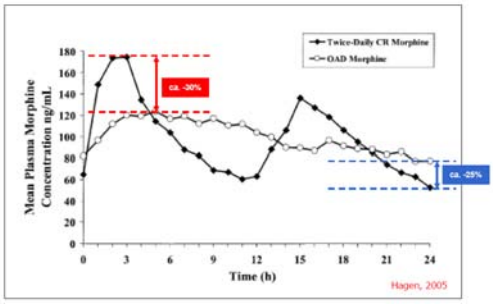
Once daily *vs.* BID (left) and *vs.* QID (right)



Fluctuation at steady state

- well-established characteristics: Peak-Trough-Fluctuation
- expectation: PTF of MR similar or less than IR product
- specific instructions for intended switching from IR to MR

Strength, variability & proportionality

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Strength(s) to be tested

- same procedure as in case of BE studies
  - linear PK of the API: study only on one dose level
  - non-linear PK: at least at highest and lowest dose level
  - IR and MR differ in linearity: additional strengths may be necessary

Between-subject variability

- should "preferably" not exceed that of the IR preparation ...
- ... or potential clinical consequences to be justified

Dose proportionality

- "should be addressed adequately" ...
- ... after single and (in case of accumulation) multiple dosing
- comparison: *"PK parameter of interest"* & dose adjustment ...
- ... *"AUC only & 25% acceptance range not acceptable"*

Factors affecting MR performance

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Interactions with food and/or ethanol

- need to be investigated (food *in-vivo*, ethanol *in-vitro*) ...
- ... significant effects may need re-formulation (if possible)
- special recommendations/requirements
  - several dose strengths: same procedure as for single-dose studies
  - impact on shape should be evaluated (profile not significantly altered)
  - clinical relevance should be discussed
  - dosing recommendations supported by specific studies

Special administration forms: "sprinkle capsules"

- beads sprinkled on soft foods, dispersed in a glass of water

Factors affecting MR performance

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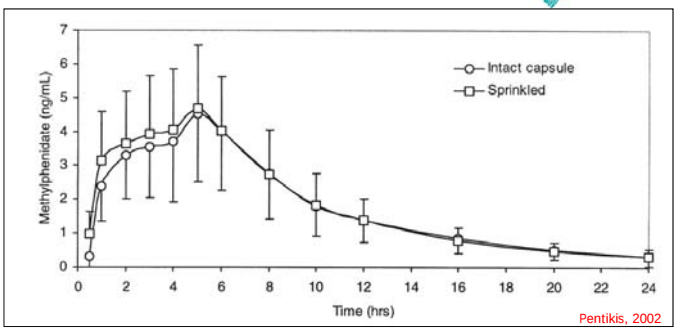

Pentikis, 2002

Special administration forms: "sprinkle capsules"

- beads sprinkled on soft foods, dispersed in a glass of water
- investigations necessary for labelling
  - additional stability and dissolution studies closed *vs.* open capsules ...
  - ... waiver/absence of *in-vivo* BE studies to be justified

Specific requirements

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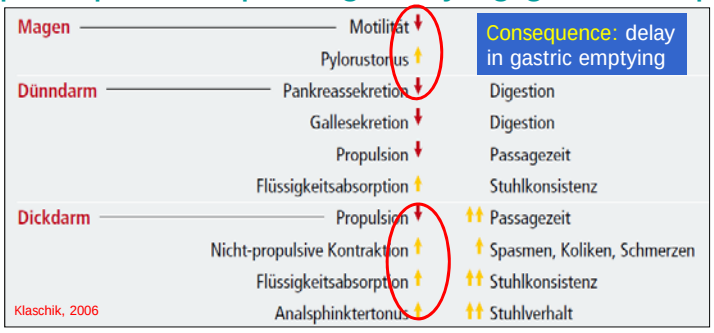
Co-administration with drugs affecting GI physiology

- necessary to investigate performance under such conditions

Example: opioids impacting/delaying gastric emptying



Specific requirements

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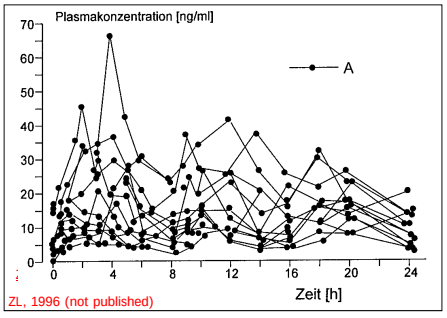
Co-administration with drugs affecting GI physiology

- necessary to investigate performance under such conditions

Example: opioids impacting/delaying gastric emptying

Morphine steady state plasma profiles



Problem

- cannot be studied in healthy subjects ...
- ... would need specific opioid antagonization ...
- ... or study in patients

Specific requirements

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Co-administration with drugs affecting GI physiology

- necessary to investigate performance under such conditions

Usual treatment of patients with altered GI function

- patients with gastroparesis (*"may need to be studied"*)
  - diabetic patients
  - patients with frequent (acute) migraine attach
- special populations ...
  - vegetarians (transit time, pH, food intake, type of food)
  - paediatric patients
  - elderly
  - patients routinely taking antacids
- *... "should be taken into consideration when designing oral once daily MR formulations"*

Therapeutic studies

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General statement/requirement

> As a principle, comparative clinical efficacy and safety data are needed in addition to PK data for modified release products developed after the immediate release formulation, unless adequately justified. As the efficacy and safety of the immediate release product is known, the major issue would be to demonstrate that the new modified release formulation is as safe and effective as the existing formulation. Additional benefits of the new formulation should be shown or justified, if claimed.

Exception(s)

- well-established concentration-effect relationship ...
- ... clinical trials may be considered unnecessary
- same or better efficacy/safety to be concluded from PK/PD

Special considerations

- rate of absorption and fluctuation may have an impact ...
- ... significance of steady-state profile shape to be considered

Waiving of therapeutic studies

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Concept/scenarios

However, therapeutic studies might be waived in case at least one of the following conditions is met:

- bioequivalence between the reference and the test product is shown in terms of $C_{max,ss}$, $C_{min,ss}$ and $AUC_{(0-\tau)ss}$ because the new modified product is developed to actually mimic the performance of product with an different release mechanism and its dosage regimen e.g. a pulsatile multiphasic release dosage form containing pellets with different lag time.
- bioequivalence between the reference and the test product is shown in terms of $C_{max,ss}$, $C_{min,ss}$ and $AUC_{(0-\tau)ss}$ despite differences in the shape of the plasma concentration-time profile if it is possible to justify that the difference in shape has no relevance for efficacy and safety based on the exposure – response and profile shape - response relationships.
- 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
  - bioequivalence between the reference and the test product is shown in terms of $AUC_{(0-\tau),ss}$
  - $C_{max,ss}$ for the new MR formulation is below or equivalent to the $C_{max,ss}$ for the appoved formulation and $C_{min,ss}$ for the MR formulation is above or equivalent to the $C_{min,ss}$ of the approved formulation.

History: metoprolol QD application

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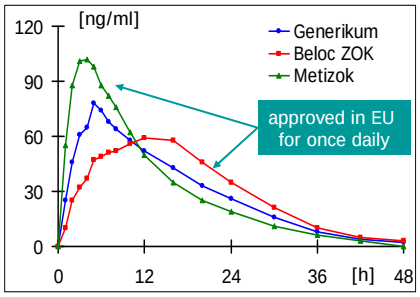
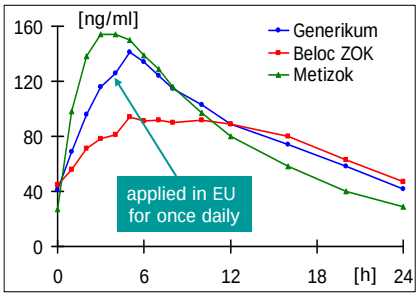
Metoprolol MR generic (Innovator: Beloc® ZOK)

- succinate (Metizok & generic) *vs.* tartrate (Beloc ZOK)

single dose profiles



multiple dose profiles



Conclusions/consequences

- generic product approved without additional clinical studies

Development of "corridor approach"

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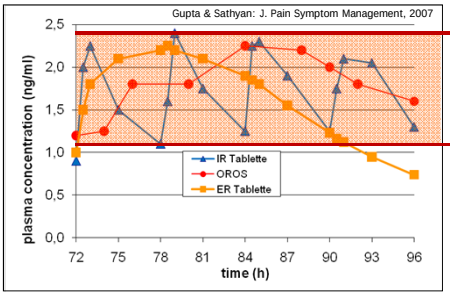
Example: hydromorphone (USA)

- development of conventional HPMC matrix tablet *vs.* OROS



"corridor" of efficacious and safe plasma concentrations (defined by IR at steady state)

Conclusions/consequences

- OROS concentrations remain in efficacious & safe corridor
- question: rate of absorption/input of therapeutic relevance?

Conclusions

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Corridor approach

- concept
  - efficacious & safe range defined/confirmed by approval of IR product
  - experimental evidence: MR form remains in corridor at steady state
- regulatory concern/questions
  - non-superior C_{max}/non-inferior C_{min} sufficient, or BE for C_{max} necessary?
  - rate of absorption essential for efficacy?

Scientific arguments/evidence

- oxcarbazepine "case"
  - clinical study confirmed insufficient efficacy for once daily...
  - ... while efficacy was equivalent/sufficient for the twice daily form
- suggestion: open minded scientific discussion ...
- ... essential to promote therapeutic progress