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Concepts and Strategies in Drug Development

MR dosage forms with special release characteristics

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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)

Special dosage/administration forms

- pellets to be sprinkled on soft food (apple sauce)
- multiphasic release dosage forms
  - biphasic release, e.g. for methylphenidate
  - pulsatile release, in order to mimic IR form given e.g. TID
- implants, vaginal devices, ...
- ... and other intramuscular/subcutaneous depot formulations
- transdermal delivery systems

Beads sprinkled on soft food

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Different type of administration

Different type of administration: The labelling of certain multiple unit formulations can recommend that the product can be opened and the pellets/beads can e.g. be sprinkled on soft foods, dispersed in a glass of non-carbonated water and swallowed without chewing or administered through a gastric tube. For the labelling to indicate this additional type of administration, additional stability and in vitro dissolution testing showing equivalence between the closed and the opened formulation is necessary. The absence of BE studies imitating the additional options of administration should be justified.

Intention

- basis: multiple unit form (pellets in capsule) ...
- ... to be opened and administered with soft food
- development goals
  - easier administration (for patients with swallowing difficulties)
  - improved consistency of profiles (more homogenous gastric emptying)

Morphine QD (pellets in capsules)

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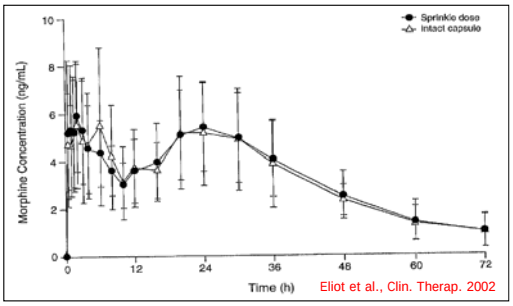
Special dosage form

- combination of different pellets: IR and ER
- goals: achieve & maintain therapeutic plasma concentrations

Single dose study: fasted *vs.* two spoons apple sauce



Eliot et al., Clin. Therap. 2002

Findings

- BE total and maximum exposure
- shape of profiles: not significantly different
- conclusion on therapeutic equivalence

Methylphenidate (pellets in capsules)

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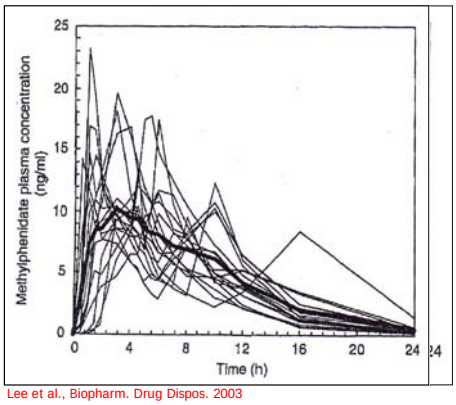
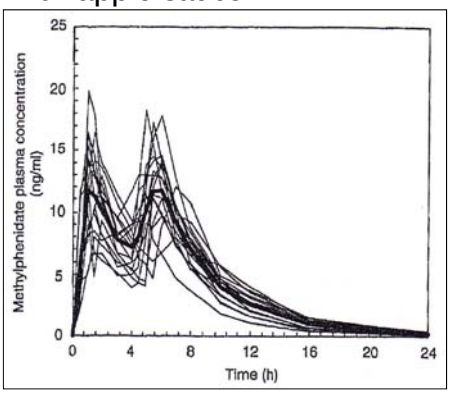
Individual plasma profiles

Ritalin® "LA": initial dose as IR, maintenance dose as ER

fasted



with apple sauce



Lee et al., Biopharm. Drug Dispos. 2003

Biphasic release preparations

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Bioequivalence assessment

> ***6.3. Multiphasic modified release products***
>
> The regulatory criteria mentioned in this Guideline are also applicable in the assessment of bioequivalence for modified release products designed to achieve sequential release combining immediate and modified characteristics (e.g. biphasic-/ pulsatile-release).

Requirements

> If one of the release phases is modified, the type and number of studies required are those described above for this specific release mechanism.
>
> However additional pharmacokinetic parameters are needed to demonstrate bioequivalence for all phases (see section 6.8.1).

Statistical evaluation

> Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $_{partial}AUC$s and C_{max} in all phases.
>
> *and in case of accumulation in
> Multiple dose: $AUC_{(0-\tau)}$, $C_{max,ss}$, $C_{\tau,ss}$

1st example: methylphenidate

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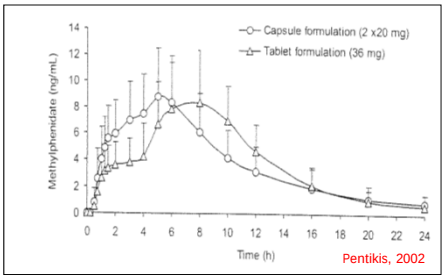
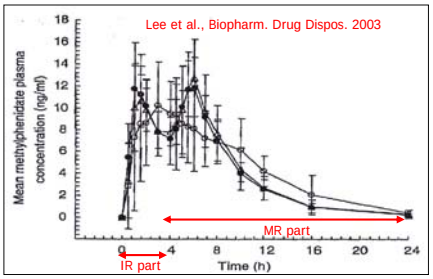
Mean plasma profiles (N=36) for BE assessment

tablet formulation (OROS) vs. pellets in capsules



Pentikis, 2002



Lee et al., Biopharm. Drug Dispos. 2003

For multiphasic modified release products additional parameters to be determined include $_{partial}AUC$, C_{max} and t_{max} in all phases. The time point for truncating the $_{partial}AUC$ should be based on the PK profile for the e.g. IR and the MR parts respectively and should be justified and pre-specified in the study protocol.

1st example: methylphenidate

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Mean plasma profiles (N=36) for BE assessment

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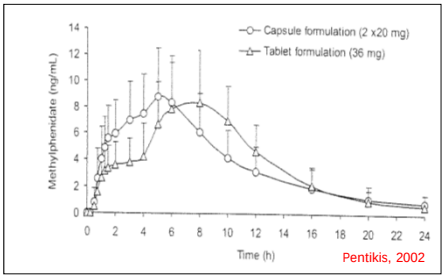

Pentikis, 2002

Findings

- BE total exposure (AUC_{0-t}) ...
- ... also for "overall" C_{max} and $AUC_{4/6-24h}$ (MR part)
- significant differences
  - exposure IR part ($AUC_{0-4/6h}$)
  - "C_{max}" IR part

For multiphasic modified release products additional parameters to be determined include $_{partial}AUC$, C_{max} and t_{max} in all phases. The time point for truncating the $_{partial}AUC$ should be based on the PK profile for the e.g. IR and the MR parts respectively and should be justified and pre-specified in the study protocol.

2nd example: oxycodone

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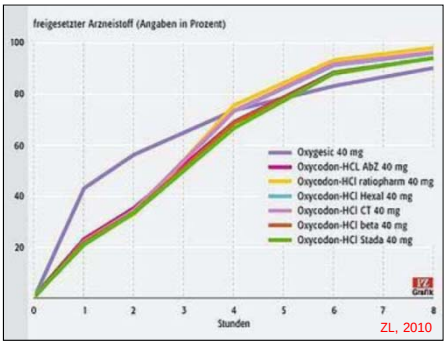
Different formulation concepts

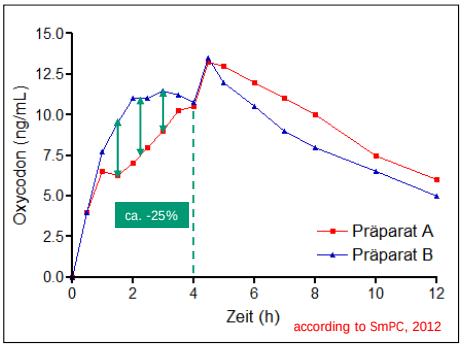
- innovator product: bi-phasic drug release ($^1/_3$ IR; $^2/_3$ ER)
- generic products in Germany: all with 100% MR

In-vitro dissolution



ZL, 2010

BA/BE generic A *vs.* innovator B



according to SmPC, 2012

2nd example: oxycodone

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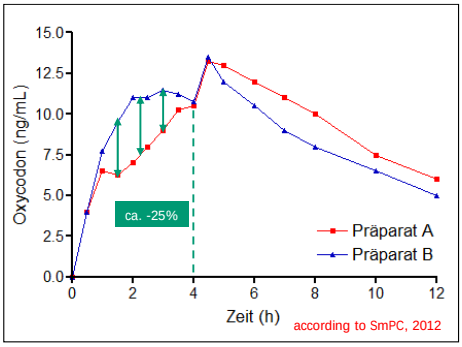
Different formulation concepts

- innovator product: bi-phasic drug release (1/3 IR; 2/3 ER)
- generic products in Germany: all 100% MR

Conclusions

- BE according "old" criteria (total AUC & absolute C_{max})
- BE not confirmed according to new regulations
  - early exposure: -25%
  - partial AUC 2nd part: +10%
  - "C_{max}" 1st part: cannot be determined for product A
  - C_{max} 2nd part: BE

BA/BE generic A *vs.* innovator B



according to SmPC, 2012

Products with pulsatile release

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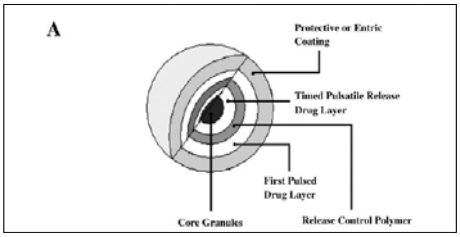
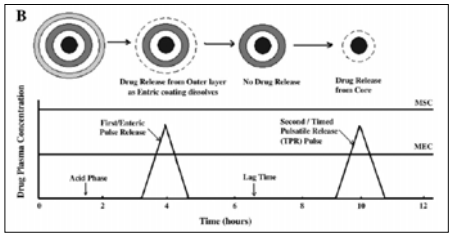
Bioequivalence assessment

5.1.5.3. Multiphasic modified release products

There are modified release preparations that have been developed solely in order to mimic a TID or QID dosage schedule. In these cases the plasma concentration - time profile of the modified release preparation should be equivalent with the immediate release formulation given in the dose schedule that is imitated unless compareable efficacy and/or safety is supported by additional clinical data.

Realistic concept ... or just a dream?





Implants, vaginal devices

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Bioequivalence assessment

6.4. Intramuscular/Subcutaneous Depot Formulations

- a single-dose study comparing test and reference products
- a multiple-dose study comparing test and reference products.

A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that:

- the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference, and consequently a low extent of accumulation is expected

Conditions

- strength to be tested
  - only one strength if proportional composition & similar dissolution
  - selected based on PK linearity/safety (non-therapeutic doses possible)
- parameters
  - no special requirements, thus conventional s.d./m.d. parameters

1st example: leuprolide

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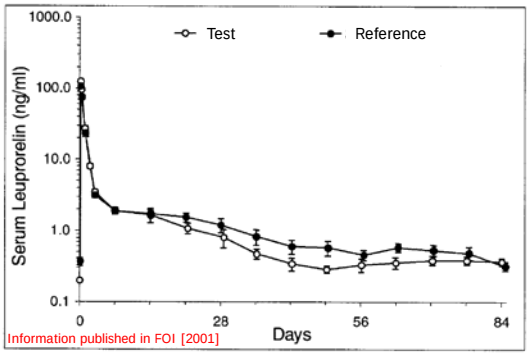
Concept/mechanism

- GnRH agonists initially stimulate testosterone secretion ...
- ... followed by long term depression ("chemical castration")

Plasma profiles (s.d., 3-month polymer suspension)



Assessment of BE

- parameters
  - total exposure ($AUC_{0\text{-}tlast}$)
  - partial AUC (0-42/42-84d)
  - maximum exposure (C_{max})
- open question:
  - initial C_{max} essential? (nota bene: "moving target", e.g. due to aging)

Early peak clinically essential?

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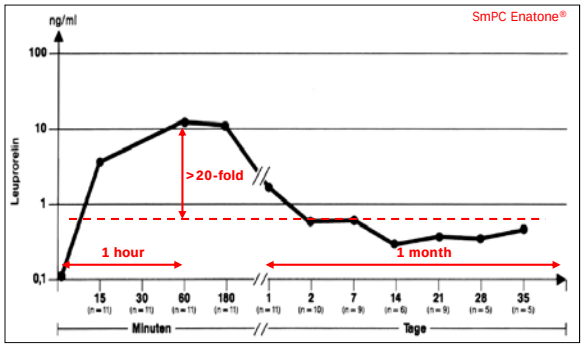
Plasma profile (s.d., 1-month polymer suspension)



Observations

- C_{max} within 1h ...
- ... down to steady-state after 1 day
- consistent plateau for rest of interval

Explanation/decision considering mechanism of action?

- GnRH agonists cause initial testosterone secretion ...
- ... followed by suppression over the entire dosing interval

PK/PD relationship?

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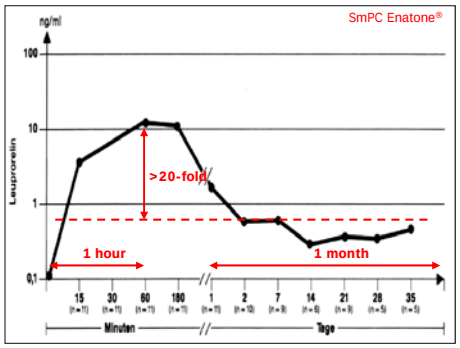
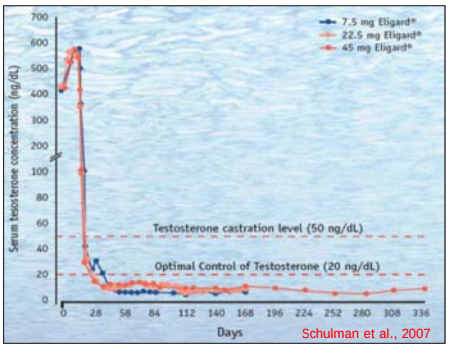
Plasma profile



Testosterone suppression



Elucidation from testosterone plasma profiles?

- peaks achieved within 2 days, castration level within 3 weeks
- necessity of initial leuprolide "burst" remains open ...

2nd example: goserelin

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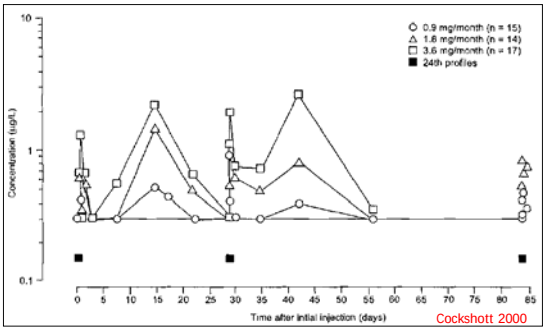
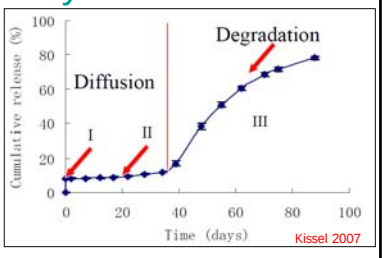
Plasma profiles (1-month product [solid implant])



Why later "burst"?



Open question

- intermediate peak relevant for efficacy and thus, BE??

2nd example: goserelin

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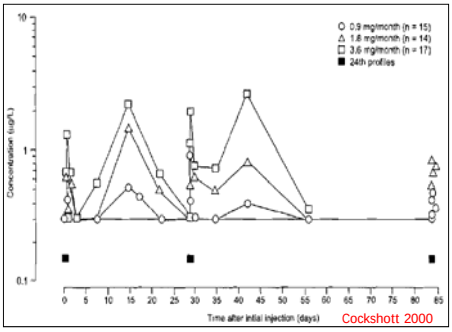
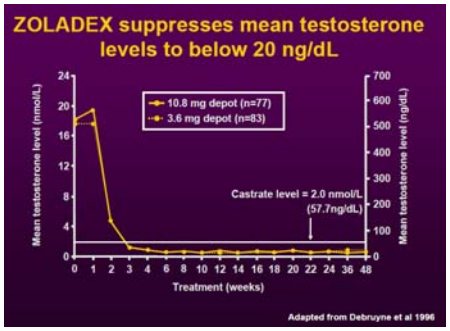
Plasma profiles



Cockshott 2000

Testosterone suppression



Open question ... and estimation

- intermediate peak relevant for efficacy?
- intermediate "burst" release obviously not necessary ...

BE assessment in case of implants

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Requirements & problem(s)

- CHMP: implants are MR forms ⇨ criteria according Guideline
  - single dose and multiple dose (if "likely to accumulate") studies
  - criteria: total and maximum exposure
- problem: how to consider burst release phenomena?

Personal view & suggestions

- standard approach "follow general BE concept" ...
- ... with exceptions, if scientifically justified, e.g. burst release
  - early C_{max} of NuvaRing®: argumentation via comparison with patch
  - late C_{max} of Zoladex®: testosterone profiles, comparison with leuprolide
- characterization of plateau phase and BE assessment
  - partial AUCs (0-½τ; ½τ-τ) as suggested by the guideline