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Bioequivalence of non-oral modified release formulations: implants and vaginally administered devices

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Regulatory requirements in Europe

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 February 2013
EMA/CHMP/EWP/280/96 Rev1

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

Draft XXIII

2. Scope

guideline deals with oral formulations, intramuscular depot formulations, subcutaneous implants, and transdermal dosage forms containing chemically defined drug substances.

Intramuscular/subcutaneous Depot formulations: A depot injection is usually a subcutaneous or intramuscular product which releases its active compound continuously over a certain period of time. Subcutaneous depot formulations include implants.

Requirements s.c./i.m. depot forms

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6.4. Intramuscular/Subcutaneous Depot Formulations

The following studies are generally required:

- 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 $AUC_{(0-t)}$ 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

First example: leuprolide

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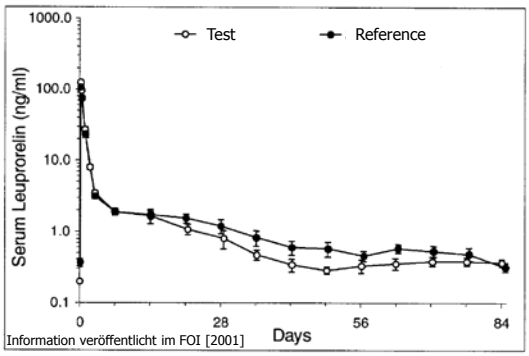
Concept/mechanism

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

Plasma profiles (3-month product)



Information veröffentlicht im FOI [2001]

How assessing BE?

- profiling entire interval
- parameters
  - total exposure ($AUC_{0\text{-}tlast}$)
  - maximum exposure (C_{max})
- open questions:
  - which C_{max} (initial, during plateau phase)?
  - early exposure essential?

How to deal with initial burst?

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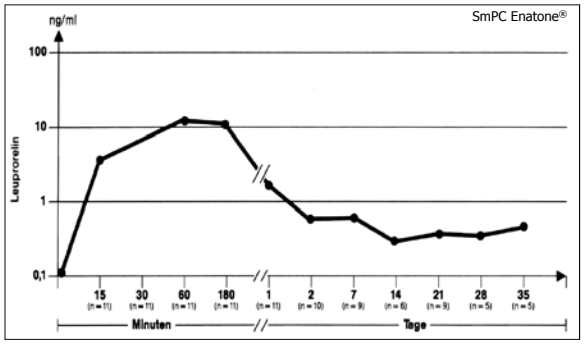
Plasma profiles (1-month product)



Observations

- initially >10-fold concentrations
- C_{max} after 1h
- rapid decrease
- down to steady-state within 1 day
- consistent plateau

Questions

- potential reasons for initial "burst" release?
- early C_{max} clinically relevant – and thus, essential for BE?

Why "burst" release?

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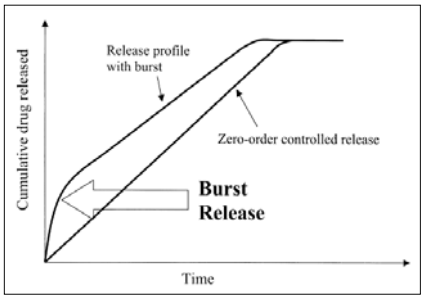
Phenomenon …

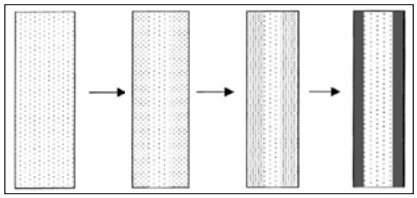
- *in-vitro* testing
  - initially accelerated release
  - subsequently controlled release (often zero-order kinetics)
- *in-vivo* consequences
  - very rapid initial drug absorption (not released in controlled manner)
  - early maximum in plasma



… background/observations

- migration of API to surface
  - due to tempering/drying
  - during storage

⇨ burst changing with time



"Burst" release clinically essential?

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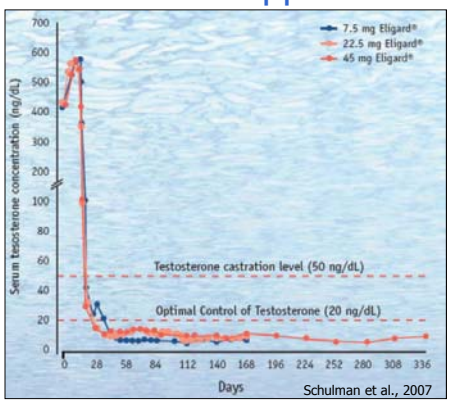
Testosterone suppression



Observations

- initial increase …
  … followed by very rapid decrease …
- … concentrations after two days below castration level
- subsequently, consistent suppression over the entire dosing interval

Conclusion

- necessity of initial leuprolide burst release remains open …

Second example: goserelin

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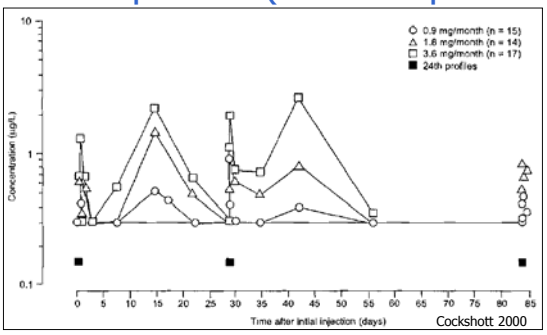
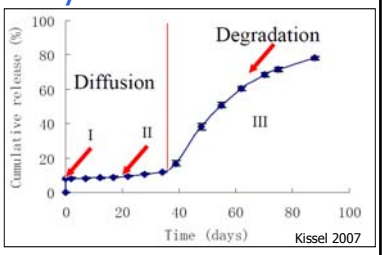
Plasma profiles (1-month product)



Why later burst?



Open questions

- intermediate maximum exposure relevant for efficacy …
- … thus, essential to be considered for BE assessment?

Intermediate "burst" clinically relevant?

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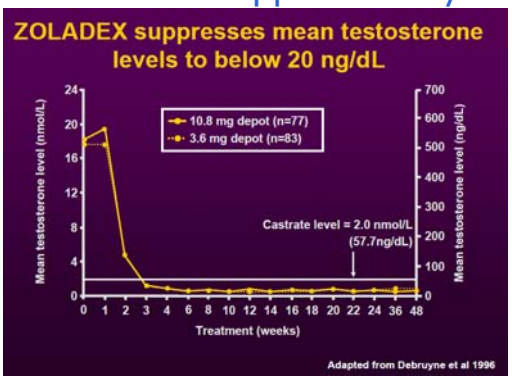
Testosterone suppression by Zoladex® (3-months)



Observations

- similar time course like leuprolide
  - initial increase …
  - … followed by rapid decrease …
  - … after two days drop below castration level
  - consistent suppression for rest of dosing interval

Conclusion (based on comparison with leuprolide)

- intermediate "burst" release obviously not necessity

Third example: NuvaRing®

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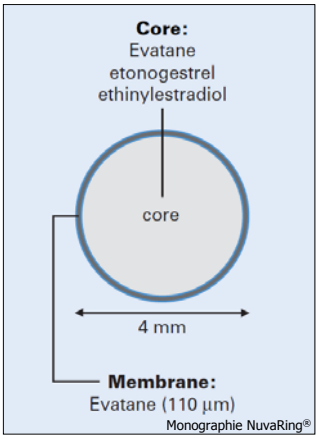
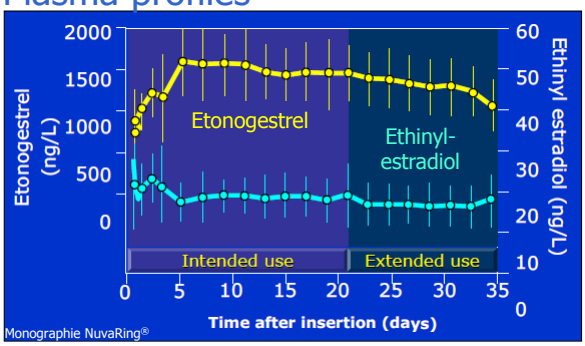
Concept & indication

- hormonal contraceptive
  - 15µg/d EE & 120µg/d ETO in vaginal device
- release controlled by membrane



Plasma profiles



Initial "burst" clinically essential?

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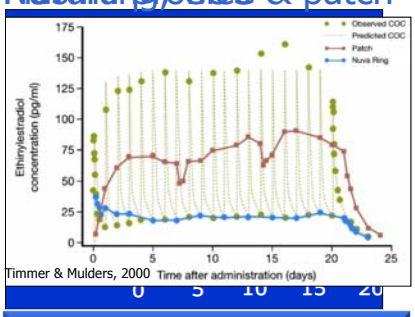
Observations & questions

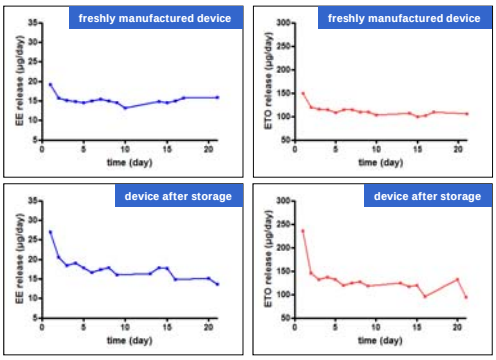
- initial rapid increase only for EE, not for ETO ⇨ why?
- early C_{max} essential for clinical efficacy?

Plasma profiles: NuvaRing, COC & patch



⇨ early C_{max} not essential

Cumulative release



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
- certain open questions: characterization of plateau phase
  - suggestion: consider partial AUC on a case-by-case basis
  - identification of C_{max} during plateau phase may be difficult/challenging