Assessment of BE of implants

Appropriate study design, metrics, and acceptance criteria

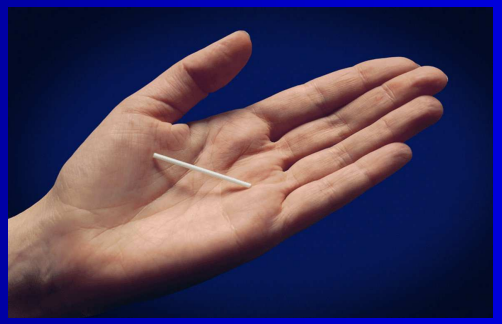
Helmut Schütz
BEBAC

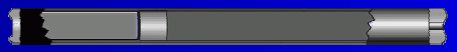
General considerations

- Implants exhibit desirable properties
  - Delivery of APIs which cannot be effectively administered via the oral route (*e.g.*, peptides, hormones,…).
  - Increased compliance compared to even OAD MR formulations.
  - Zero-order input (*i.e.*, constant delivery rate) lead to steady-state plasma levels with little fluctuations.
  - More cost-effective health care delivery (*e.g.*, reduced number of visits to the physician for s.c. depot injections).

General considerations

- Desirable properties…
  - Steady-state levels preserved if implants are changed.
  - Drug quickly eliminated after removal of implant; no ‘tail’ effect like after depot injections.





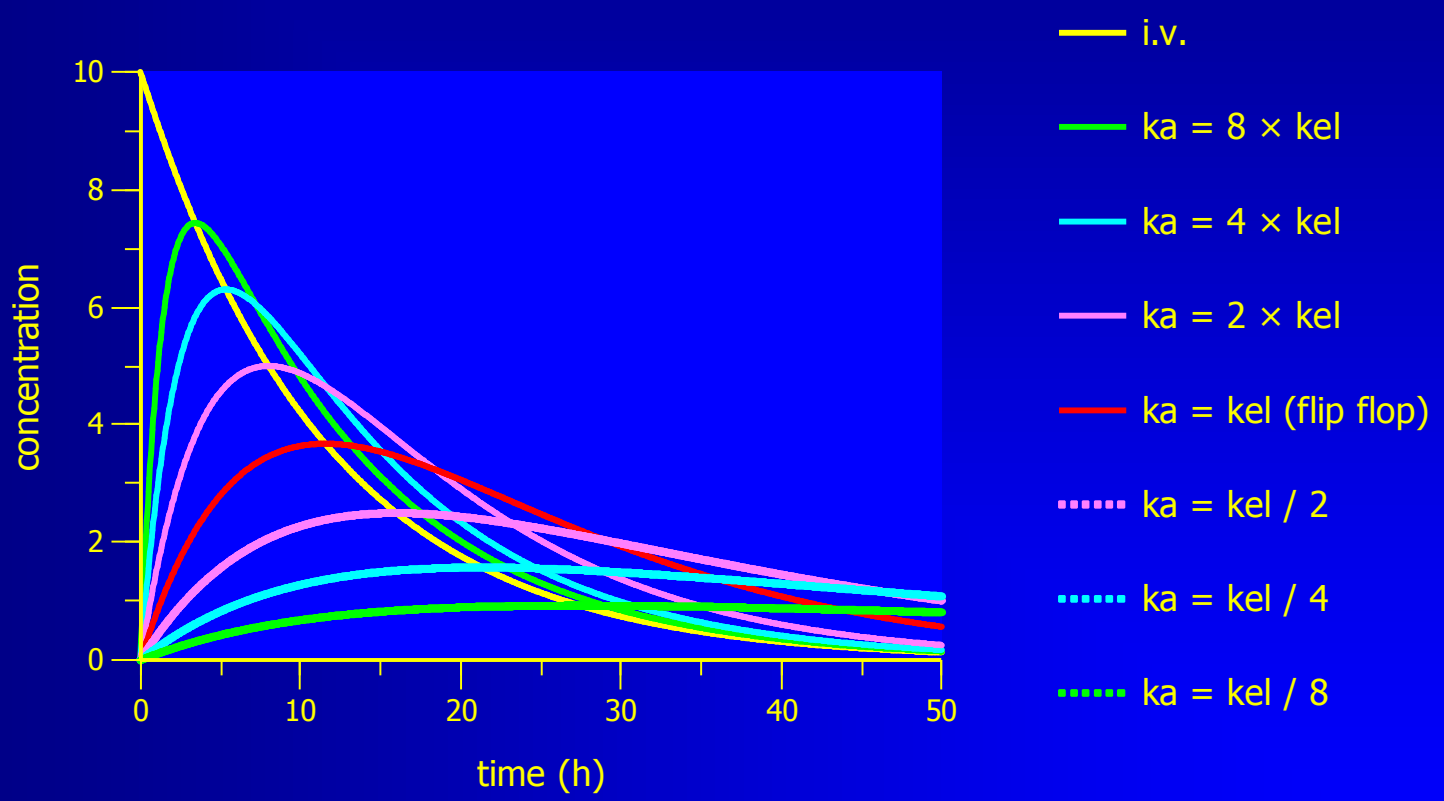
General considerations

- Problems
  - *In vitro* release for manufacturing QC difficult to standardize.
  - Insertion procedures invasive with a wide range of applications (from s.c. to implantation of drug-eluting stents).
  - Pharmacokinetic characterisation of *in vivo* data far from trivial in many cases. Metrics commonly applied in BE (AUC, C_{max}) estimated by noncompartmental methods (NCA) not always suitable.

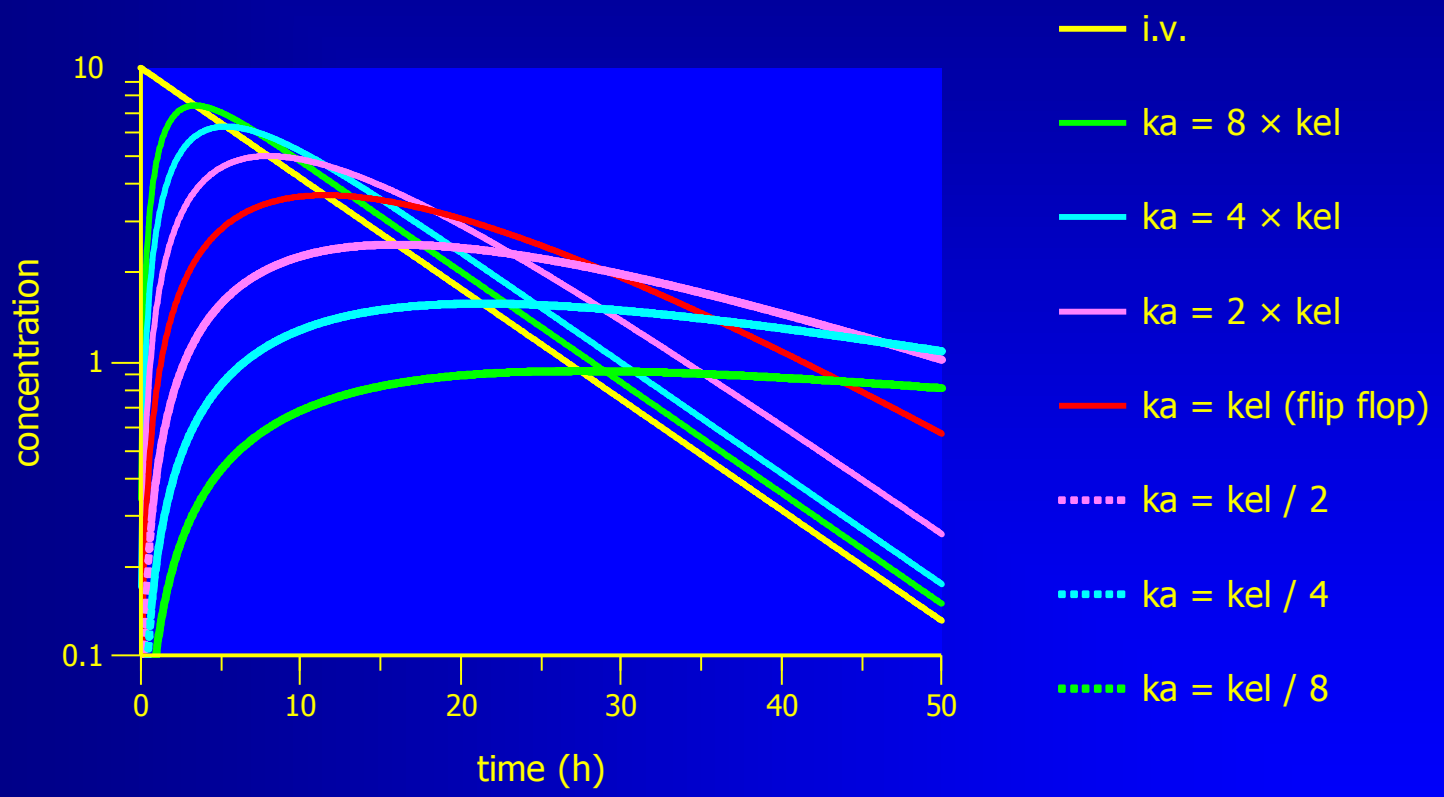
General considerations

- Problems
  - Cross-over design not suitable if implant is kept in place for long time – or is not intended to be removed at all.
  - Parallel designs challenging (low statistical power, sequential designs difficult).

Excursion into PK



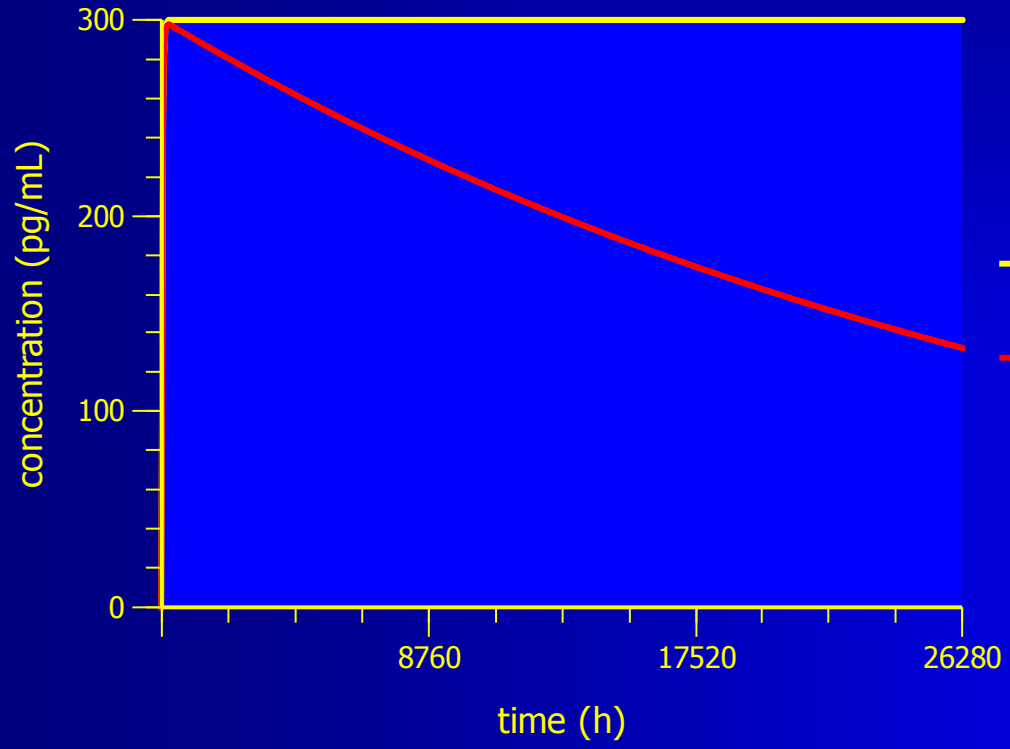
Excursion into PK



SD – Steady State

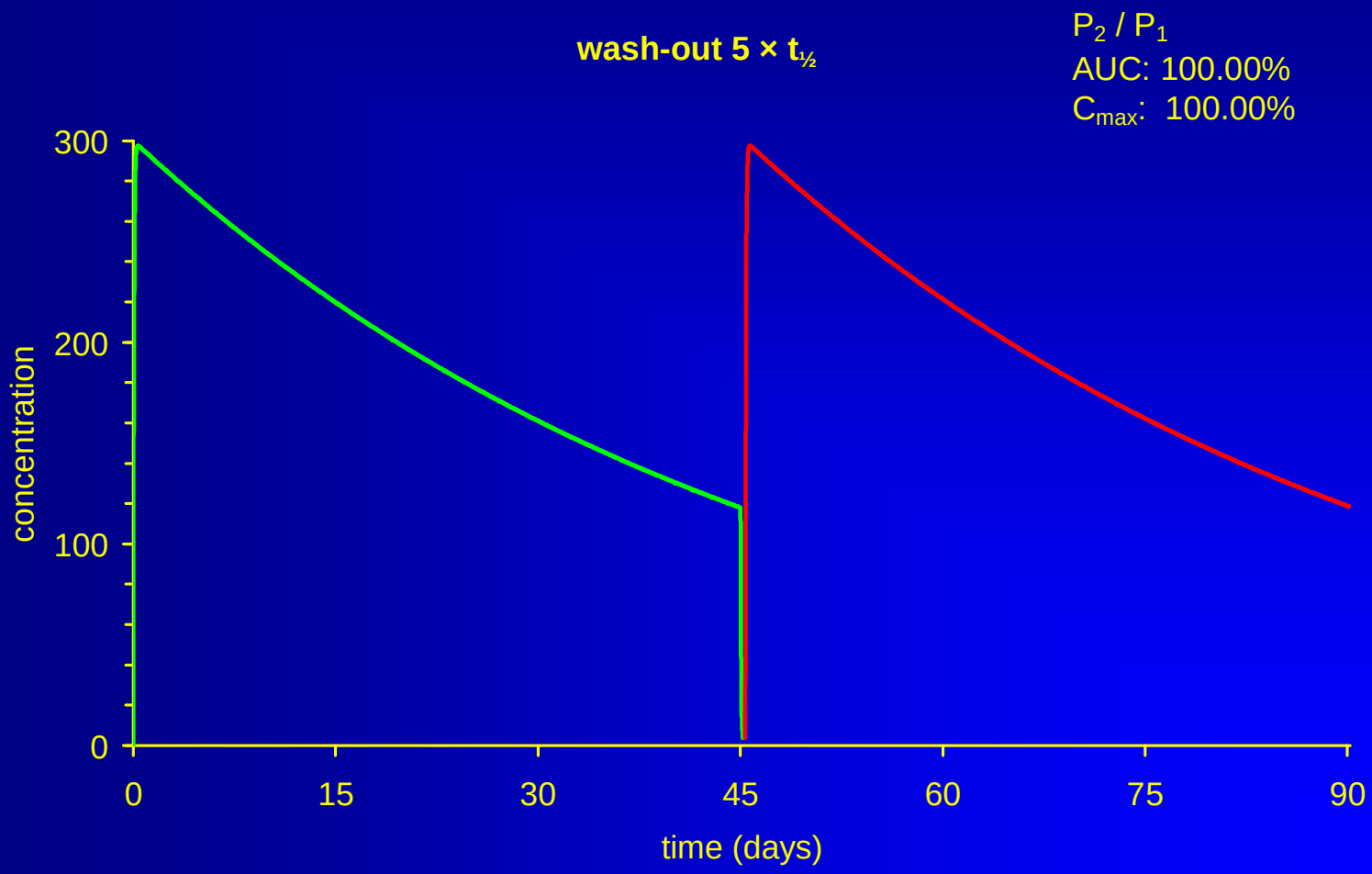
- Single dose studies generally considered to be most sensitive in detection differences between formulations
  - Any zero-order input will lead to steady state; time to reach state state dependent on the ratio of input rate and k_{el}.
  - Flip-flop PK: 'terminal phase' represents *input rate* rather than k_{el}.
  - If input rate ≠ zero order, but decreasing, profile *looks* like common *first order* input! *No extrapolation*; AUC from t = 0 to timepoint of removal.

Hormonal implant

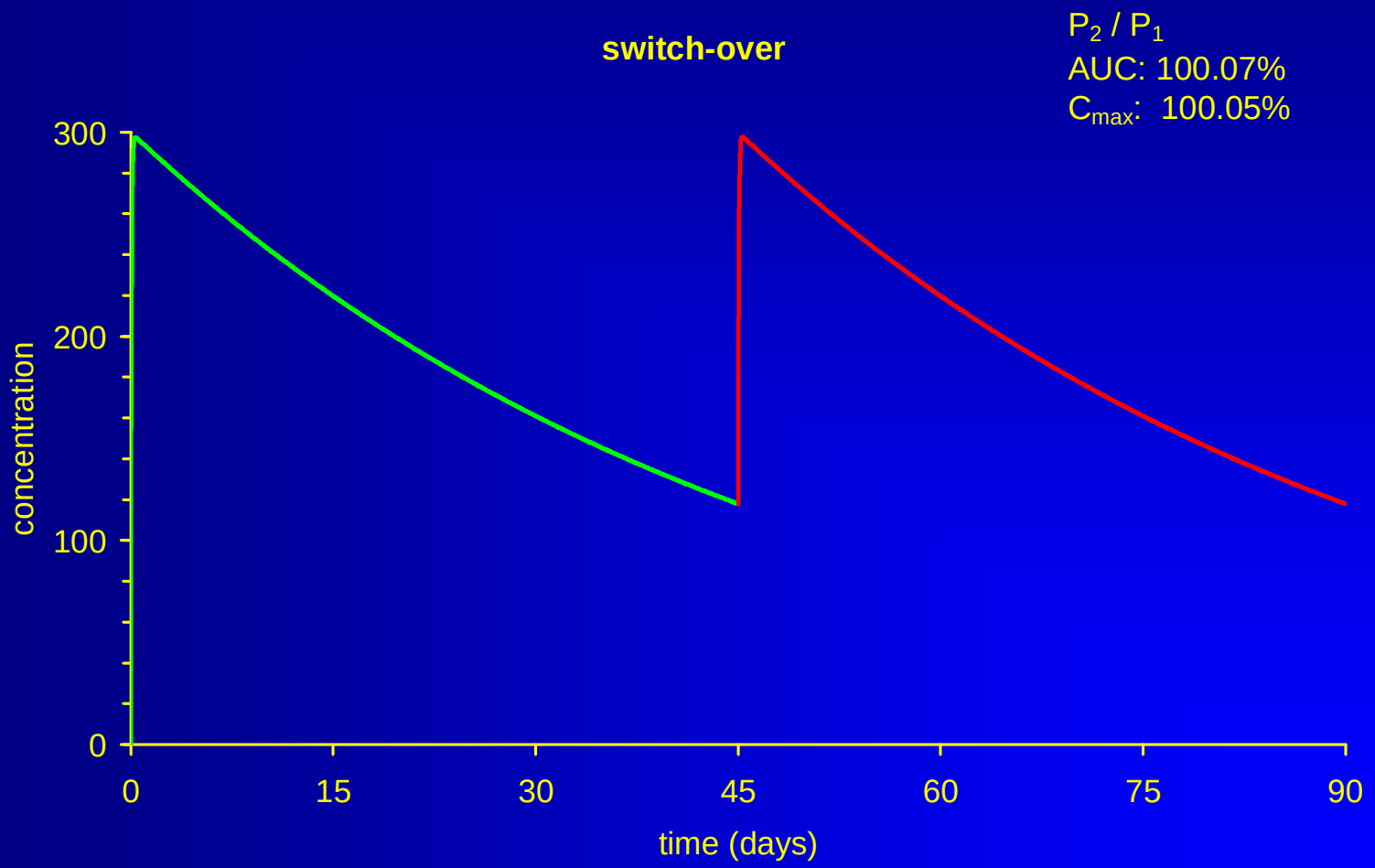


68 mg etonogrestel
Release rate decreasing from 60–70 µg/d after insertion to 40 µg/d at start of 2nd year and 25–30 µg/d at the end of the 3rd year.

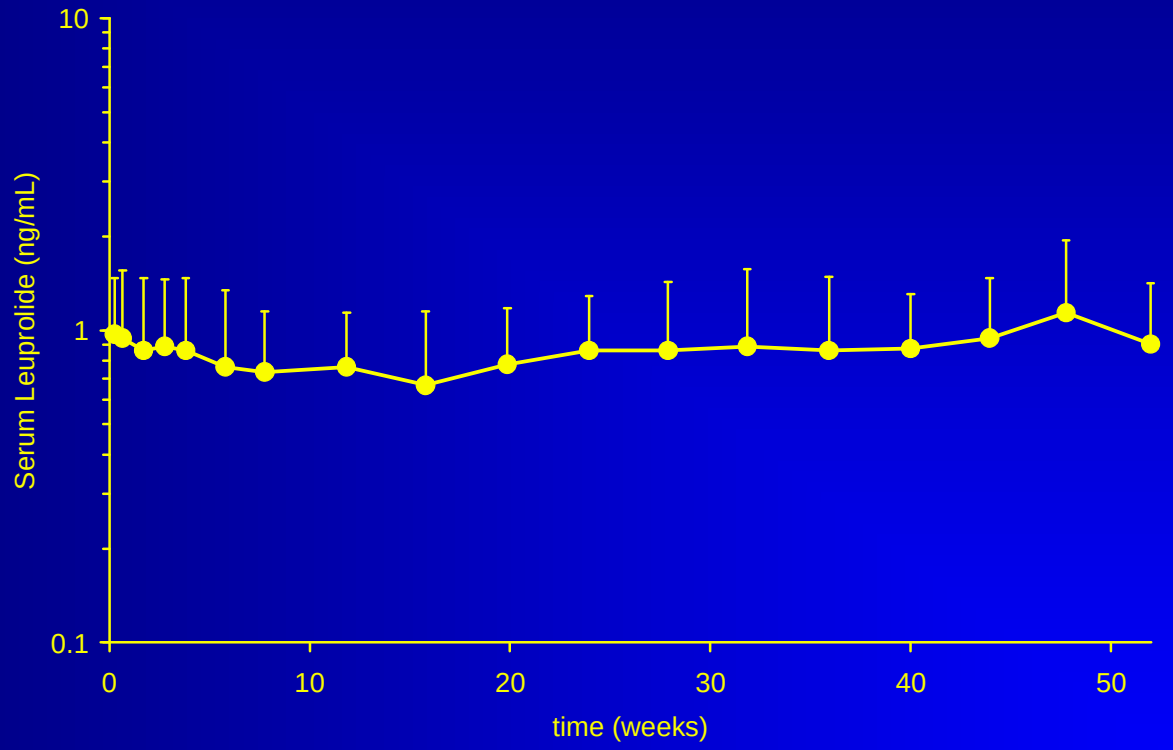
Wash-out *vs.* Switch-over



Wash-out *vs.* Switch-over



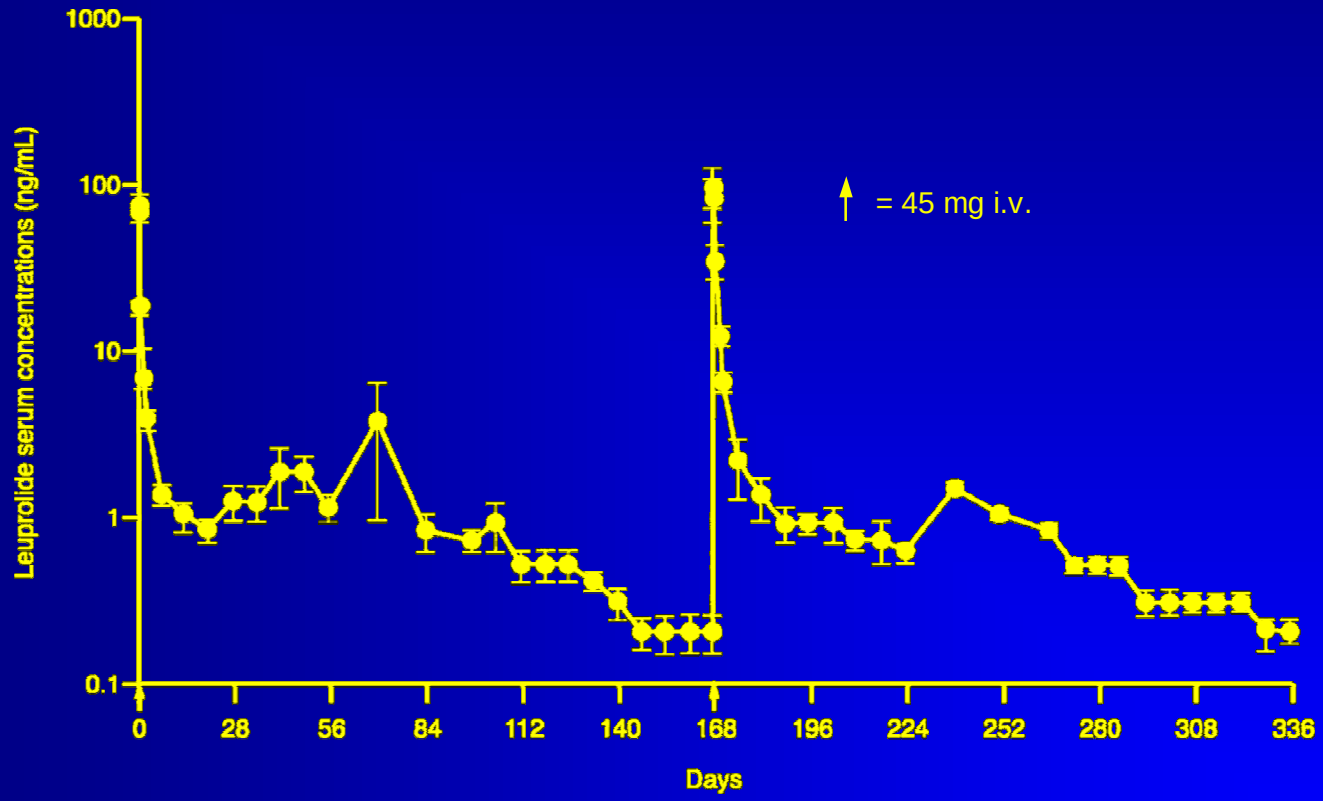
Leuprolide Osmotic Pump



Mean + SD (n=27)

Wright JC, Leonard ST, Stevenson CL, Beck JC, Chen G, Jao RM, Johnson PA, Leonard J, Skowronski RJ
An in vivo/in vitro comparison with a leuprolide osmotic implant for the treatment of prostate cancer
J Control Rel 75(1-2), 1–10 (2001)

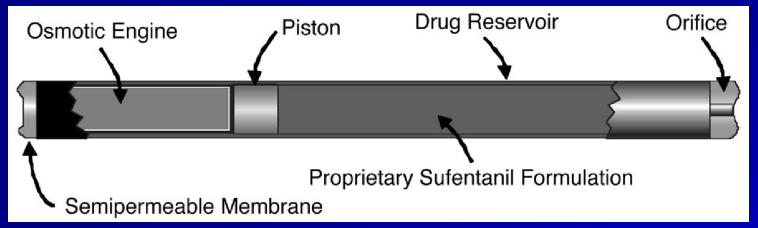
Leuprolide Osmotic Pump

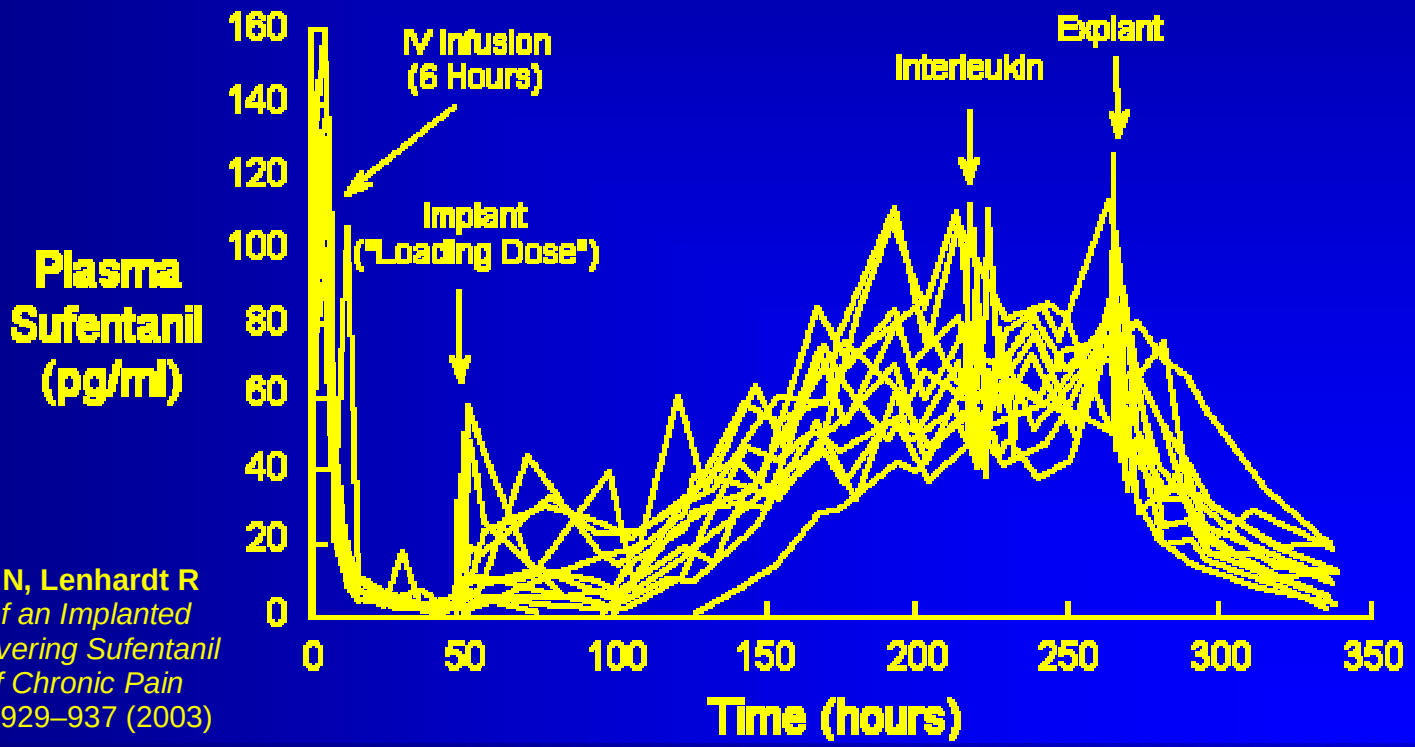


Crawford ED, Sartor O, Chu F, Perez R, Karlin G, Garrett JS
A 12-month clinical study of LA-2585 (45.0 mg): a new 6-month subcutaneous delivery system for leuprolide acetate for the treatment of prostate cancer
J Urol 175(2), 533–536 (2006)

Mean ± SD (n=28)

Sufentanil Osmotic Pump





Fisher DM, Kellett N, Lenhardt R
Pharmacokinetics of an Implanted Osmotic Pump Delivering Sufentanil for the Treatment of Chronic Pain
Anesthesiology 99, 929–937 (2003)

Metrics

- Extent of absorption / total exposure
  - AUC
  - No extrapolation to t = ∞ if implant is removed.
- Rate of absorption / peak exposure
  - For strict zero-order input and decreasing input rate C_{max} of doubtful value – might occur at any time within the sampling interval due to random fluctuations (‘apples-and-oranges’ statistics).
  - C_{max} useful for implants showing a lag-time or mixed input (first-order/zero-order).

Metrics

- Rate of absorption / peak exposure
  - Peak-to-Trough Fluctuation
  - C_{min} only if clinically relevant (example: 0.1 ng/mL leuprolide $\rightarrow$ <50 ng/dL testosterone)
    Global C_{min} within the sampling interval – not at the end (C_{trough})!
  - Partial AUC?
  - Characterization of input function by deconvolution / PopPK modeling. Regulatory acceptance?

Design Challenges

- Mainly studies in patients
- Cross-over not feasible for implants intended for long-term use or changes in disease state (carry-over)
- Parallel groups lack statistical power
- Whenever possible, additional PD data should be considered

Statistical Challenges

- *A priori* sample size estimation required for pivotal studies
  - Pilot studies not feasible due to long duration
  - Sequential designs problematic (second stage after interim analysis doubles run time)
  - Interim analysis for early stopping?
- Cross-over not feasible for implants intended for long-term use or changes in disease state (carry-over)

Statistical Challenges

- Substantial variability require large sample sizes for conventional BE acceptance range (AR)
  - Reference scaling requires replicate cross-over
  - *A priori* widening of ARs – based on clinical data?
  - For implants with short-time use (*e.g.*, 1–2 weeks) PK metrics may be corrected for actual clearance, either by an i.v. dose prior to adminstration or by simultaneous i.v. adminstration of a stable isotope.

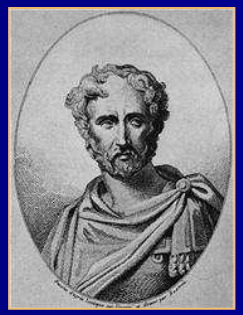
Thank You!

Assessment of bioequivalence of implants

Helmut Schütz
BEBAC
Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria
helmut.schuetz@bebac.at

To bear in Remembrance...

The fundamental cause of trouble in the world today is that the stupid are cocksure
while the intelligent are full of doubt. *Bertrand Russell*



In these matters the only certainty is
that nothing is certain.
Gaius Plinius Secundus (Pliny the Elder)

It is a good morning exercise for a research scientist
to discard a pet hypothesis every day
before breakfast.
It keeps him young. *Konrad Lorenz*