Assessment of bioequivalence of implants: Appropriate study design, metrics, and acceptance criteria

Assessment of BE of implants

Appropriate study design, metrics, and acceptance criteria

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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, $C_{\text{max}}$) 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).
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Excursion into PK

- i.v.
- $ka = 8 \times kel$
- $ka = 4 \times kel$
- $ka = 2 \times kel$
- $ka = kel$ (flip flop)
- $ka = kel / 2$
- $ka = kel / 4$
- $ka = kel / 8$

[i.v. line graph with concentration on the y-axis and time (h) on the x-axis, showing various $ka$ values leading to different concentration profiles over time]
Excursion into PK

![Graph showing PK concentration over time for different $ka$ values: i.v., $ka = 8 \times kel$, $ka = 4 \times kel$, $ka = 2 \times kel$, $ka = kel$ (flip flop), $ka = kel / 2$, $ka = kel / 4$, $ka = kel / 8$.](image-url)
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 $\neq$ 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 etonogestrel
Release rate decreasing from 60–70 µg/d after insertion to 40 µg/d at start of 2\textsuperscript{nd} year and 25–30 µg/d at the end of the 3\textsuperscript{rd} year.
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**Wash-out vs. Switch-over**

- wash-out $5 \times t^{1/2}$
- $P_2 / P_1$
- AUC: 100.00%
- $C_{max}$: 100.00%

Graph showing concentration over time (days) with wash-out and switch-over periods.
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Wash-out vs. Switch-over

P₂ / P₁
AUC: 100.07%
Cₘₐₓ: 100.05%
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Leuprolide Osmotic Pump

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)

Mean + SD (n=27)
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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

Mean ± SD (n=28)
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Sufentanil Osmotic Pump

Fisher DM, Kellett N, Lenhardt R
Metrics

- Extent of absorption / total exposure
  - AUC
  - No extrapolation to t = \( \infty \) if implant is removed.

- Rate of absorption / peak exposure
  - For strict zero-order input and decreasing input rate
    \( C_{\text{max}} \) of doubtful value – might occur at any time within the sampling interval due to random fluctuations (‘apples-and-oranges’ statistics).
  - \( C_{\text{max}} \) useful for implants showing a lag-time or mixed input (first-order/zero-order).
Metrics

- Rate of absorption / peak exposure
  - Peak-to-Trough Fluctuation
  - $C_{\text{min}}$ only if clinically relevant (example: 0.1 ng/mL leuprolide $\rightarrow$ <50 ng/dL testosterone)
    - Global $C_{\text{min}}$ within the sampling interval – not at the end ($C_{\text{trough}}$)!
  - 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
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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 administration or by simultaneous i.v. administration of a stable isotope.
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Thank You!

Assessment of bioequivalence of implants

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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*