The Predictive Power of Dissolution and Alternatives to Full Bioequivalence

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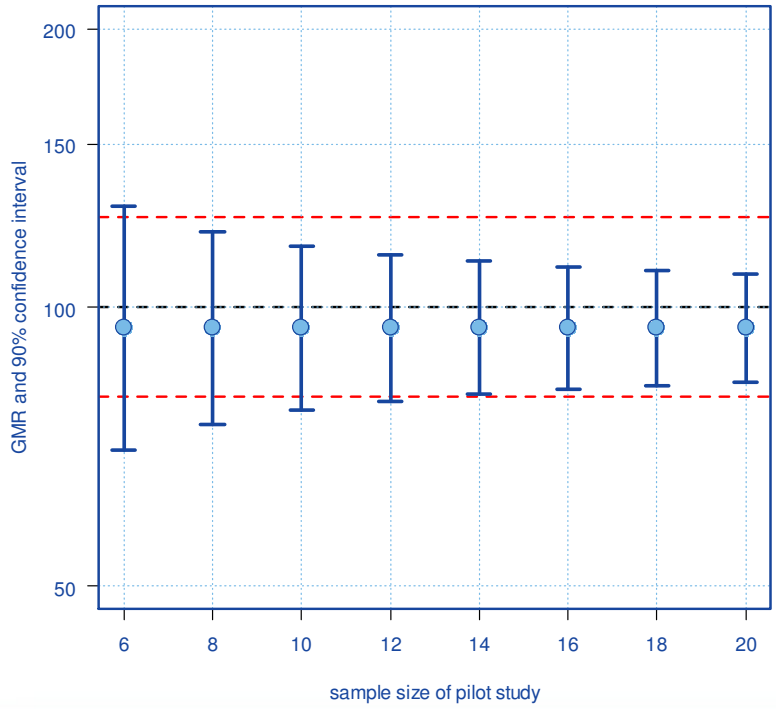
Pilot PK studies

Power and size.

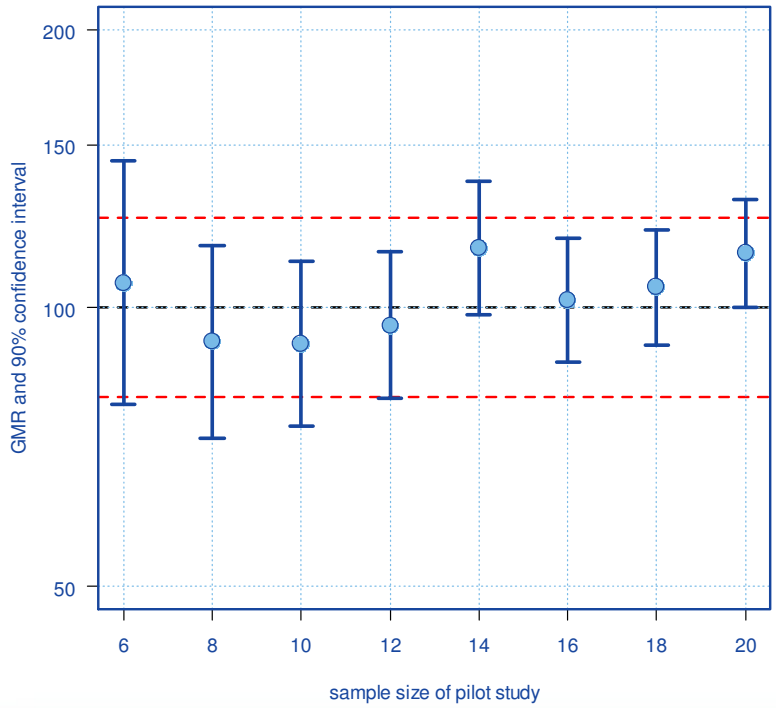
- By definition pilot studies are exploratory in nature; hence, they have no ‘power’.
  - It is tempting to keep the sample size as small as possible (six subjects were recommended in the last century).
  - Simulations with *GMR* 0.95.
  - The ‘true’ *GMR* lies with probability α within the 90% CI.
  - With increasing sample size, the CI narrows.
  - It may be even possible to show BE (*e.g.*, for the FDA).
  - Is it *that* simple?
    - Is it realistic to expect *identical GMR*s in *different* studies?



Pilot PK studies

Power and size.

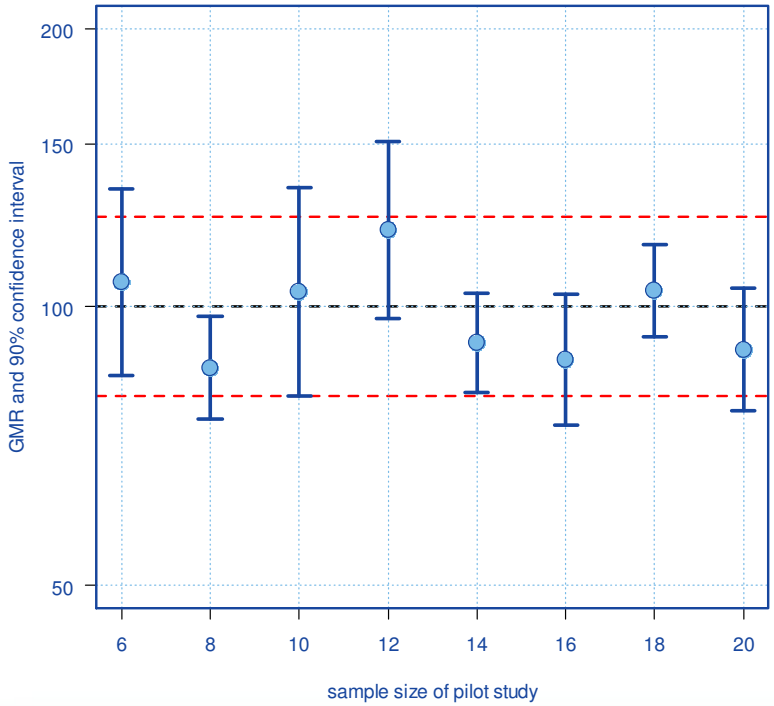
- Let us be more realistic:
  - Studies are done in different subjects. Therefore, we would expect that the *GMR*s will vary between studies as well.
  - If we compare different studies, the between-subject variability will hit (the *GMR* follows a log-normal distribution and I assumed that $CV_{inter} = 2 \times CV_{intra}$).
  - Is this the end of the tunnel?
    - Could we expect that the within-subject *CV* will remain constant?
    - Maybe we should go even one step further.



Pilot PK studies

Power and size.

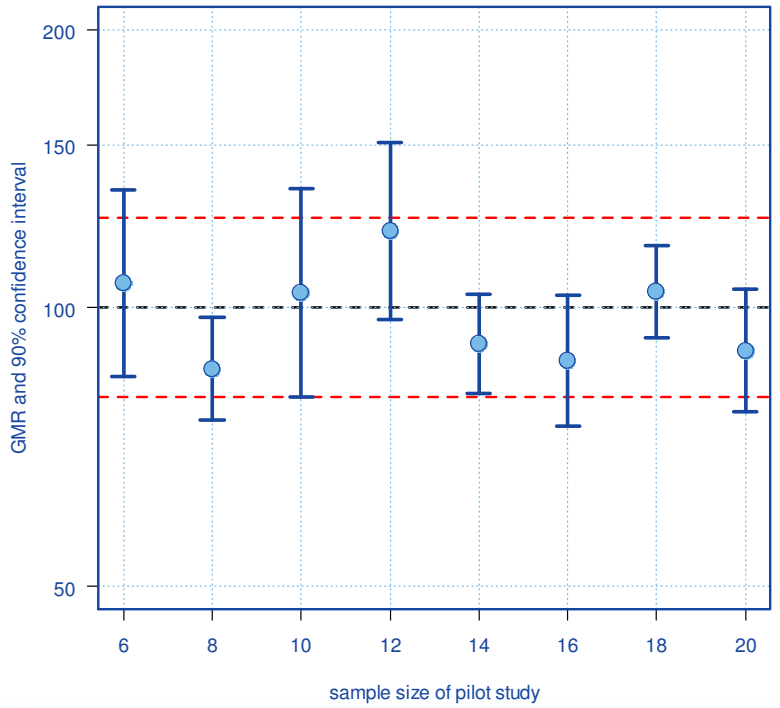
- Let us be more realistic:
  - Now we allow the within-subject variability also to vary (the variance follows a χ^2 distribution).
  - Unfortunatelly *this* is what we can expect from pilot studies.
    - Sometimes we get a false impression of low variability (*e.g.*, with $n = 8, 14, 18$).
    - Sometimes we get a false impression of almost perfectly matching products (*e.g.*, with $n = 10, 18$).
  - To get *reliable* estimates of both the *GMR* and the *CV* we would have to perform pilot studies which a *larger* than the pivotal one!



Pilot PK studies

Power and size.

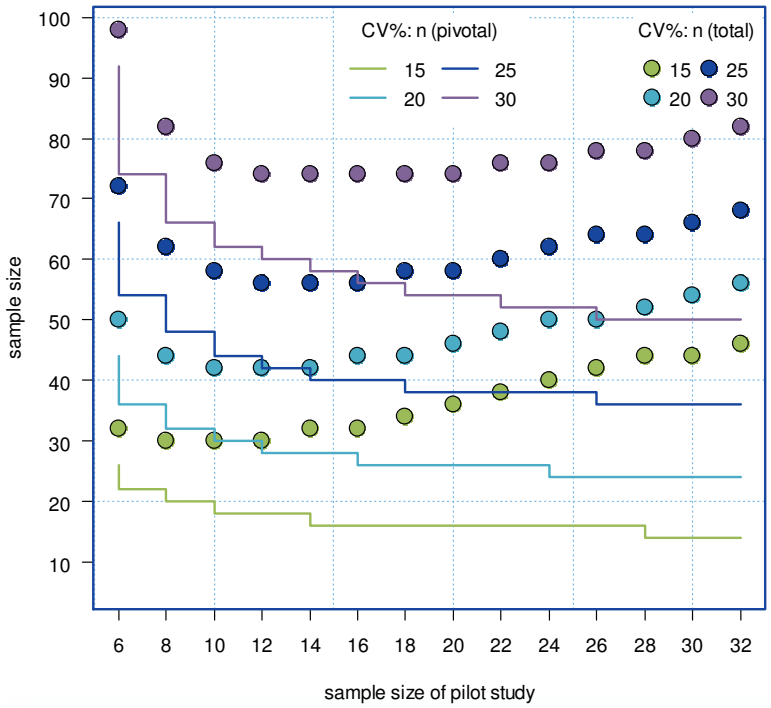
- Let us explore the details:
  - The *GMR* in the pilot study with 12 subjects is 121%.
    - Should we trash the formulation since the *GMR* is that close to the upper BE-limit – or not?
    - We know the true value: 95%!
  - The *CV* in the pilot study with 10 subjects is 32%.
    - Is this a HVD(P)?
    - We know the answer: No!
    - Particularly nasty. If we aim for reference-scaling (RSABE/ABEL) we would need a smaller sample size (compared to ABE). If in the pivotal the *CV* turns out to be <30% we would not be allowed to scale and will be *underpowered* for ABE.



Pilot PK studies

Sample size based on upper CL of the *CV* in the pilot

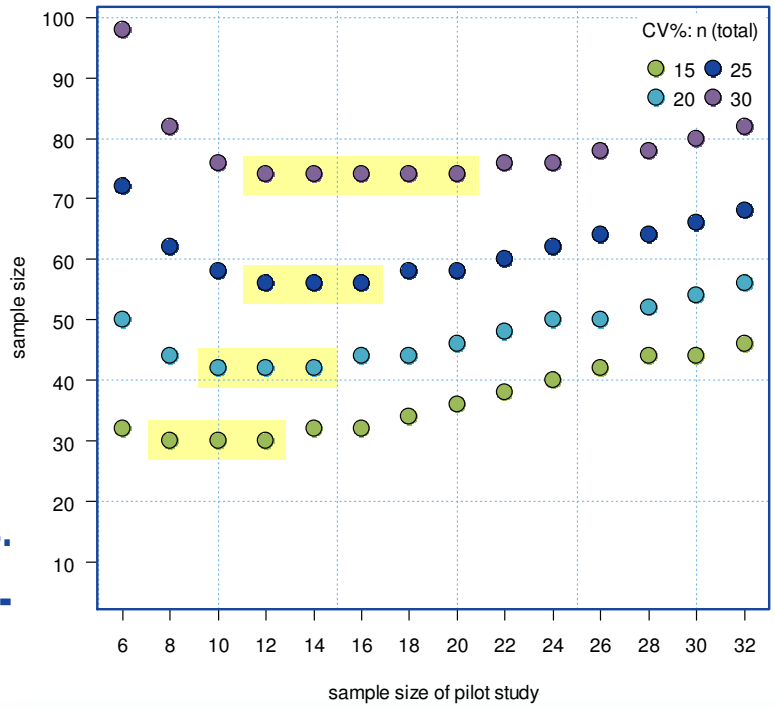
- The larger the pilot, the more precise the estimated *CV*.
  - Its upper CL will be more close to the estimate.
  - Hence, the sample size of the pivotal study will be *smaller*.
  - Very small pilots are practically use-less (due to the more imprecise *CV*).
  - Examples
    - *CV* 15%, pilot sample size 12.
      - » Upper CL of the *CV* 19.1%.
      - » Sample size of pivotal 18 (total 30).
        'Carved in stone': 12 (24).
    - *CV* 25%, pilot sample size 16.
      - » Upper CL of the *CV* 30.6%.
      - » Sample size of pivotal 40 (total 56).
        'Carved in stone': 28 (44).



Pilot PK studies

Sample size based on upper CL of the *CV* in the pilot

- The larger the pilot, the more precise the estimated *CV*.
  - However, we have to pay for both studies.
    - It seems that there are minima in the total sample sizes (dependent on the *CV*).
    - Can we conclude that there is an 'ideal' size of a pilot study? The smaller the better?
    - We also want to get a precise estimate of the *GMR*.
      - » Opt for a pilot size at the *upper* end of the 'ideal' range (or slightly larger).
    - If you suspect a HVD(P), perform the pilot in a replicate design to estimate the CV_{wR}.
      - » Some companies' policy for HVDP(s) is a full replicate in at least 24 subjects.
    - Don't use the 'carved in stone' *CV* and perform a power analysis (Session 4, part I).



Pilot PK studies

Does statistics help at all?

- To some extent, yes. See Fuglsang (2015) for further information.
- Caveats
  - The most critical value is the *GMR* – which is difficult to assess in a pilot study.
    - » Charles DiLiberti (2016) presented an example taking the worst case (pilot study in 12 subject; upper CL of *CV* 25% and *GMR* 0.95) into account. This would result in a 'perfect' pivotal sample size of 128 [*sic*] subjects.
  - Never assume perfectly matching products.
    - » The batch release spec's are ±5% of the declared content.
    - » Ask the QC lab about the accuracy and precision of the method (excellent ones have ~2.5%). The GL requires T- and R-batches deviating in content ≤5%. Even if you are extremely lucky to find batches with a *measured* content of 100% the *true* content may differ by 100 – 100 (97.5 / 102.5) ~ 5%.
  - Two-Stage Designs deal only with the *CV*. Allow for a safety margin of the *GMR*.

Fuglsang A. *Pilot and Repeat Trials as Development Tools Associated with Demonstration of Bioequivalence.* AAPS J. 2015; 17(3): 678–83. DOI 10.1208/s12248-015-9744-6.
DiLiberti C. *Adaptive Design Bioequivalence Studies: Controlling the Type 1 Error Rate While Preserving Power.* Rockville, 14–16 September, 2016: *The Global Bioequivalence Harmonization Initiative: EUFEPS/AAPS 2nd International Workshop.*

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Thank You!

Open Questions?

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