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Breaking through boundaries

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FDA slides

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Potential area of investigation-Long approved RLDs

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- Many of the FDA PSGs relate to RLDs that were approved decades ago
- AS such the Functional relationships of CMA/CPP to CQA was never understood with an absence of defined design space
- This result is no real understanding of Q3 and the influence of manufacturing and age i.e. solutions that become suspensions and vice versa
- The FDA in vitro bioequivalence PSGs guidance does its job and as such these RLDs are failing the guidance between batches and over time (ageing)
- We have also found that the RLD batch to batch and age variability is influenced by the physicochemical properties of the drug (e.g. poorly soluble) and the formulation strength (e.g. 0.05%, etc)
- Extremely low concentrations (<0.1 ng/ml) in receiver fluid results in increased variability
- BLQ or zero values cannot be reported due to log transformation of data
- How to best hit a moving target?

RLD Ageing Comparison – Compound A

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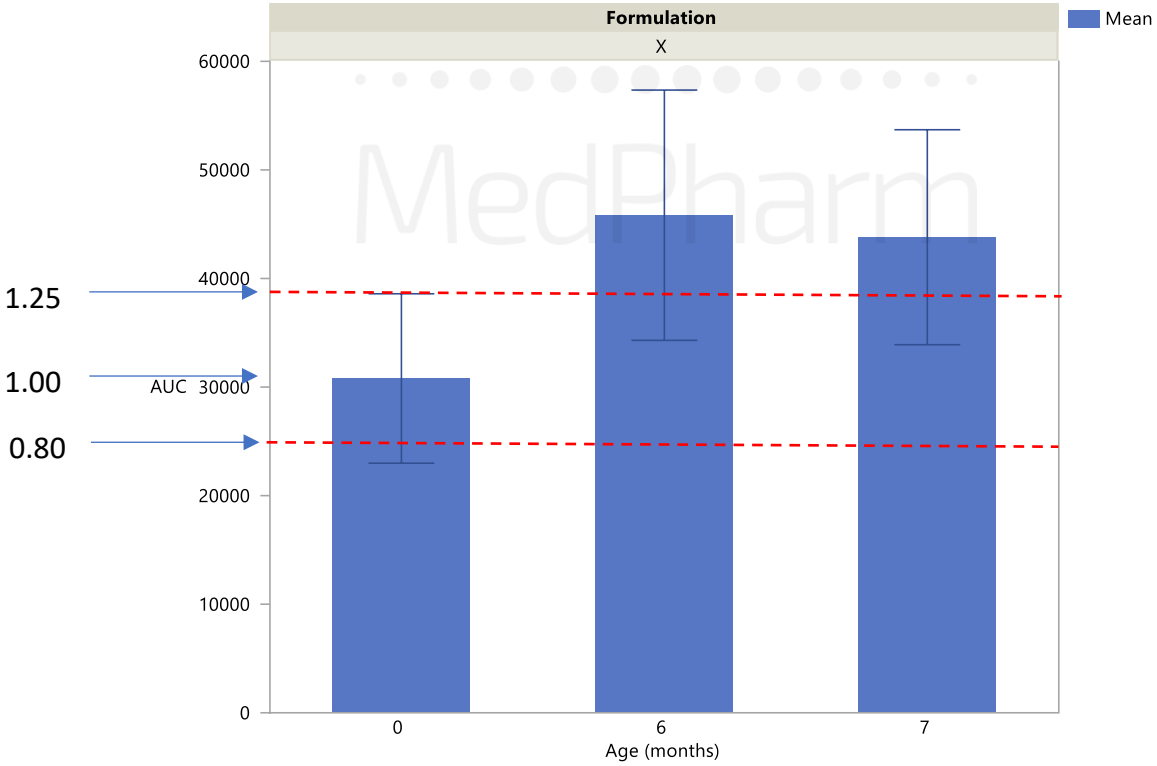
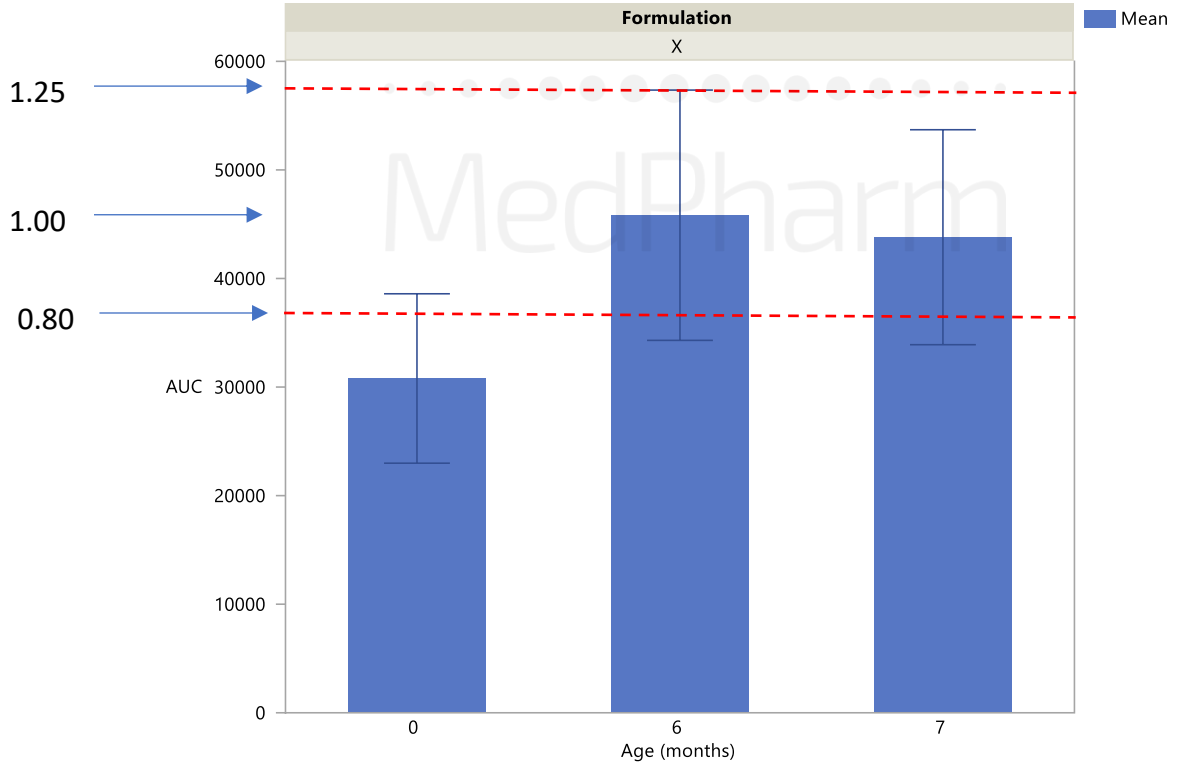
Mean(AUC) vs. Age (months)



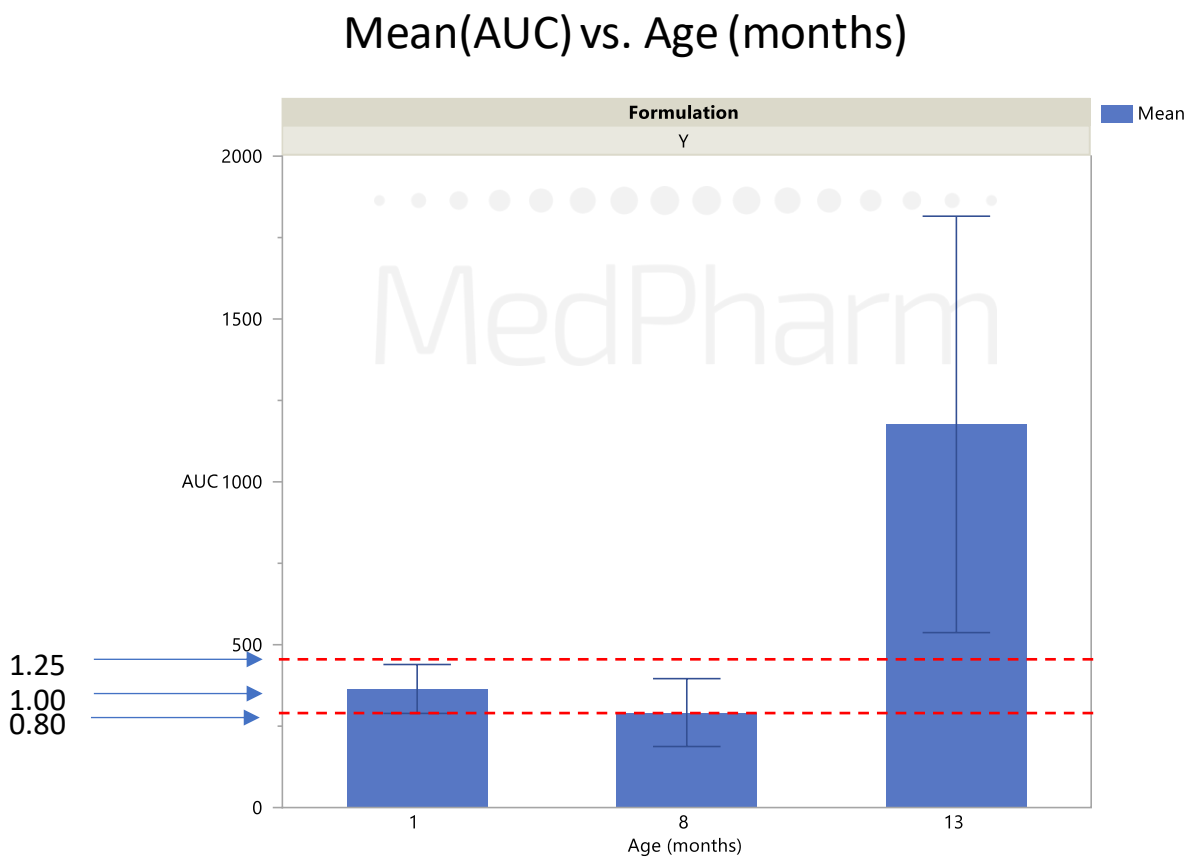
- 3 batches of RLD Compound A
- Mean ± 90% CI.
- Red dotted lines are the BE limits for the 0 month formulation

Mean(AUC) vs. Age (months)



- 3 batches of RLD Compound A
- Mean ± 90% CI
- Red dotted lines are the BE limits for the 6 month formulation

RLD Ageing Comparison – Compound B



- 1 batch of RLD Compound B
- 3 different times
- Mean ± 90% CI
- Red dotted lines are the BE limits for the 1 month formulation