Notice: Proposed Policy on Bioequivalence Standards for Highly Variable Drug Products

June 26, 2015

Our file number: 15-107147-494

This Notice serves to inform sponsors of drug submissions pursuant to Division C.08 of the Food and Drug Regulations [that is (i.e.), new drug and abbreviated new drug submissions] of proposed changes in Health Canada's comparative bioavailability requirements for drug products which exhibit large pharmacokinetic within-subject variation in extent of absorption, as measured by area under the concentration versus time curve (AUC).

Previous Health Canada guidance has emphasized study design to address the challenges presented by highly variable drug products (HVDPs). Nevertheless, Health Canada's view has continued to evolve with ongoing external consultations on this issue. Health Canada recognises that when the within-subject variation of a pharmacokinetic parameter is high, a larger number of subjects must be recruited in order to meet the usual bioequivalence standard of the 90% confidence interval within the bioequivalence interval of 80.0-125.0%. Other regulatory agencies have also recognised the issue with HVDPs and have developed approaches to reduce the number of subjects required to meet their regulatory standards.

Further to recommendations made by Health Canada's Scientific Advisory Committee on Pharmaceutical Sciences and Clinical Pharmacology, in June 2014, Health Canada has reviewed various approaches and is proposing to adopt an average bioequivalence approach to HVDP with expanding limits based on the within-subject variability of the reference product. The proposed approach would permit widening of the bioequivalence interval for AUC, with a point estimate constraint. A drug product may be considered a HVDP if the within-subject coefficient of variation (CV) of the AUC for the reference product is greater than 30.0%. Critical dose drugs are not eligible for the application of this approach of widening the bioequivalence intervals.

Evidence from the literature, or the results of well conducted studies, should be provided to indicate that the AUC is highly variable. The proposal for widening the bioequivalence interval should be defined a priori in the study protocol. A scientific rationale should be provided to support that the high variability in exposure is not clinically significant. Submissions for HVDPs should also be supported by a justification to demonstrate that the CV estimates are reliable and not subject to the influence of outliers.

For HVDPs, replicate design comparative bioavailability studies should be conducted with the reference product (R) administered at least twice to determine the within-subject variability for the reference product. The test product (T) should be administered either once in a 3-period design (RTR, TRR, RRT) or twice in a 4-period design (TRTR, RTRT).
The lower and upper limits of the expanded bioequivalence interval for the 90% confidence interval should be calculated using the within-subject standard deviation of the log-transformed values of AUC of the reference product (sWR). Expansion of the 90% confidence limits may be permitted up to a maximum sWR of 0.472 (equivalent to a CV of 50.0%).

For HVDPs, the following comparative bioavailability standards should be met:

1. The 90% confidence interval of the relative mean AUC of the test to reference product should be within the following limits:
   a. 80.0%-125.0%, if $s_{WR} \leq 0.294$ (i.e., CV $\leq$ 30.0%),
   b. $\left[ \exp(-0.76s_{WR}) \times 100.0\% \right] - \left[ \exp(0.76s_{WR}) \times 100.0\% \right]$ if $0.294 < s_{WR} \leq 0.472$ (i.e., 30.0% $< CV \leq$ 50.0%), or
   c. 69.8%-143.2%, if $s_{WR} > 0.472$ (i.e., CV $>$ 50.0%);

2. The relative mean AUC of the test to reference product should be within 80.0% and 125.0% inclusive;

3. The relative mean maximum concentration ($C_{max}$) of the test to reference product should be between 80.0% and 125.0% inclusive.

Reference


Health Canada is posting this Notice for a sixty day comment period. Please send comments to:

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1 The AUC to which the HVDP criteria and expanded confidence limits will apply is the AUC subject to bioequivalence standards, as specified in the Health Canada guidance document *Comparative Bioavailability Standards: Formulations Used for Systemic Effects* (2012).

2 As defined in the Health Canada guidance document *Comparative Bioavailability Standards: Formulations Used for Systemic Effects* (2012).
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