Bioequivalence evaluation of epinephrine autoinjectors with attention to rapid delivery

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Abstract: Timely and proper injection of epinephrine is critical to prevent serious consequences relating to anaphylaxis. In a recent bioavailability study comparing epinephrine delivery from the Auvi-Q™ and EpiPen® epinephrine autoinjectors, the Auvi-Q failed to meet the bioequivalence threshold when using partial area under the curve (AUC) analyses based on zero to T\text{max} recommended for highly variable drugs such as epinephrine. Peak plasma epinephrine concentrations for the EpiPen occurred 10 minutes (median T\text{max}) after dosing, while peak concentrations for the Auvi-Q occurred 20 minutes after dosing. Though bioequivalence may be concluded for C\text{max}, AUC\text{inf}, and AUC\text{0–t}, for fast-acting therapeutics used to treat life-threatening conditions, such as epinephrine, additional pharmacokinetic parameters such as AUC zero to T\text{max} may be important to evaluate when assessing bioequivalence.

Keywords: anaphylaxis, therapy, pharmacokinetics, bioavailability, EpiPen, T\text{max}
mended by the FDA for high-variability substances such as epinephrine (ie, intrasubject variability > 30%). Seventy-one individuals were included in the pharmacokinetic (PK) data analysis; 67 individuals received dosing with Auvi-Q, while 69 subjects received at least one dose using the EpiPen.

The primary PK parameters for BE assessment were peak drug concentration (C_max) and area under the curve (AUC); baseline correction was performed to adjust for endogenous levels of epinephrine. Secondary partial AUC parameters were also determined for each individual’s concentration–time profiles by calculating the AUC from time zero to the time of the maximum plasma concentration (T_max) after injection with the EpiPen. Partial AUC values were higher for the EpiPen than for the Auvi-Q. As shown in Table 1, BE may be concluded for C_max and concentration–time curve from baseline extrapolated to infinity (AUC_infinity) and AUC from baseline extrapolated to infinity (AUC_infinity). However, BE was not concluded for the partial AUC analyses based on zero to T_max of reference after first administration (R1ACOTMX) or based on zero to T_max of reference after second administration (R2ACOTMX).

Further, based on median T_max parameters, peak epinephrine concentrations for EpiPen occurred 10 minutes after dosing (0.170 hours, range 0.07–1.00) while peak concentrations for Auvi-Q occurred 20 minutes after dosing (0.330 hours, range 0.07–1.00). While this difference was not considered significant, a numeric T_max difference may be highly critical to the therapeutic efficacy of epinephrine administration.

The PK parameters C_max, AUC_0–t, and AUC_infinity for Auvi-Q and EpiPen, which met the equivalence criteria using the baseline-corrected data set, were presented by Edwards et al at the American Academy of Allergy, Asthma, and Immunology annual meeting. This presentation did not specifically comment on partial AUC analyses, which failed to meet the BE threshold. However, given the clinical significance of rapid epinephrine delivery, additional PK parameters such as T_max and partial AUC analysis may be considered as a requirement for BE. When there is a need for rapid absorption of a life-saving medication, in the case of fast-acting, highly variable therapeutics, additional PK factors might be important to evaluate when assessing BE.

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References


Table 1 Baseline corrected results for comparison of Auvi-Q™ (Sanofi, Bridgewater, NJ, USA) to EpiPen® (Mylan Specialty LP, Basking Ridge, NJ, USA) autoinjectors

<table>
<thead>
<tr>
<th>PK parameters</th>
<th>Ratio</th>
<th>Lower</th>
<th>Upper</th>
<th>μ_T – μ_R</th>
<th>σ_wr^2</th>
<th>Upper 95% confidence limit for (μ_T – μ_R)^2 – 0.8 σ_wr^2</th>
<th>CV_wr (%)</th>
<th>Criterion 1: confidence limit</th>
<th>Criterion 2: point estimate</th>
<th>Bioequivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max}</td>
<td>0.9446</td>
<td>0.8439</td>
<td>1.0844</td>
<td>–0.0570</td>
<td>0.1931</td>
<td>–0.0146</td>
<td>43.94</td>
<td>Pass</td>
<td>Pass</td>
<td>Yes</td>
</tr>
<tr>
<td>AUC_{0–t}</td>
<td>1.1544</td>
<td>1.0575</td>
<td>1.2774</td>
<td>0.1436</td>
<td>0.1279</td>
<td>–0.0373</td>
<td>35.76</td>
<td>Pass</td>
<td>Pass</td>
<td>Yes</td>
</tr>
<tr>
<td>AUC_{infty}</td>
<td>1.1747</td>
<td>1.0915</td>
<td>1.3693</td>
<td>0.1610</td>
<td>0.1250</td>
<td>–0.0179</td>
<td>35.36</td>
<td>Pass</td>
<td>Pass</td>
<td>Yes</td>
</tr>
<tr>
<td>R1ACOTMX</td>
<td>0.7635</td>
<td>0.6549</td>
<td>0.9219</td>
<td>–0.2698</td>
<td>0.3494</td>
<td>–0.0686</td>
<td>59.11</td>
<td>Pass</td>
<td>Fail</td>
<td>No</td>
</tr>
<tr>
<td>R2ACOTMX</td>
<td>0.7896</td>
<td>0.6585</td>
<td>0.9532</td>
<td>–0.2362</td>
<td>0.3154</td>
<td>–0.0670</td>
<td>56.16</td>
<td>Pass</td>
<td>Fail</td>
<td>No</td>
</tr>
</tbody>
</table>


Abbreviations: AUC_{0–t}, area under the concentration–time curve from baseline to last measurable concentration in ng ⋅ h/mL; AUC_{infty}, area under the concentration–time curve from baseline extrapolated to infinity in ng ⋅ h/mL; C_{max}, peak drug concentration in ng/μL; CV_wr, coefficient of variation for reference (EpiPen®) in percent; PK, pharmacokinetic; R1ACOTMX, partial AUC based on zero to T_max after first administration in ng ⋅ h/mL; R2ACOTMX, partial AUC based on zero to T_max after second administration in ng ⋅ h/mL; T_max, time at maximum plasma concentration in hours; μ_T, mean of reference (EpiPen®); μ_R, mean of test (Auvi-Q); σ_wr^2, intrasubject variability for reference.

