Note

Different Truncation Methods of AUC between Japan and the EU for Bioequivalence Assessment: Influence on the Regulatory Judgment

Masayo OISHI, Koji CHIBA*, Takashi FUKUSHIMA, Yoshiro TOMONO and Toshio SUWA

Department of Drug Development Science & Clinical Evaluation, Keio University Faculty of Pharmacy, Tokyo, Japan

Full text of this paper is available at http://www.jstage.jst.go.jp/browse/dmpk

Summary: In regulatory guidelines for bioequivalence (BE) assessment, the definitions of AUC for primary assessment are different in ICH countries, i.e., AUC from zero to the last sampling point (AUCall) in Japan, AUC from zero to infinity (AUCinf) or AUC from zero to the last measurable point (AUClast) in the US, and AUClast in the EU. To assure sufficient accuracy of truncated AUC for BE assessment, the ratio of truncated AUC (AUCall or AUClast) to AUCinf should be more than 80% both in Japanese and EU guidelines. We investigated how the difference in the definition of truncated AUC affects BE assessment of sustained release (SR) formulation. Our simulation result demonstrated that AUCall/AUCinf could be ≥80% despite AUClast/AUCinf being <80% and AUCall failed to detect formulation difference. In Japanese package inserts of generic drugs in SR formulation, there were products for which AUCall/AUCinf was ≥80% though AUClast/AUCinf was <80%. In conclusion, it was confirmed that the difference in definition of truncated AUC affected the judgment of validity of truncated AUC for BE assessment, and AUCall could fail to detect the substantially different in vivo dissolution profile of generic drugs with SR formulation from the original drug.

Keywords: drug development; clinical pharmacokinetics; bioequivalence; regulatory science; sustained release formulation; AUC

Introduction

Bioequivalence (BE) between a generic product and its original product is assessed based on the comparison of exposure, i.e., maximum plasma/serum concentration (Cmax) and the area under concentration-time curve (AUC). Cmax and AUC are indicators of the rate and extent of absorption, respectively. In regulatory guidelines for BE assessment in International Conference on Harmonization (ICH) countries,1-3 the criterion to judge BE is that the 90% confidence interval (CI) of the ratio of geometric means of Cmax and AUC should be within 80–125%. The same approach to assess BE is taken in the ICH countries; however, the definitions of AUC for primary assessment are different (Table 1), i.e., AUC from zero to the last sampling point (AUCall) is allowed in Japan,1 AUC from zero to infinity (AUCinf) or AUC from zero to the last measurable point (AUClast) in the US,2 and AUClast in the EU.3 In Japan and the EU, truncated AUC (AUCall or AUClast) should be used for the primary BE assessment. To assure sufficient accuracy to assess the extent of exposure using truncated AUC for BE assessment, the ratio of truncated AUC (AUCall or AUClast) to AUCinf should be more than 80% in Japan and the EU (Fig. 1),1,3 despite the definition of truncated AUC is different (Fig. 2). When all the concentrations are above the lower limit of quantitation (LLOQ), AUCall equals

<table>
<thead>
<tr>
<th>Country/region</th>
<th>Definition of AUC for primary BE assessment</th>
<th>The criteria to assess BE using truncated AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>AUC from 0 to last sampling time (t) (AUCall)</td>
<td>AUCall should be more than 80% of AUCinf</td>
</tr>
<tr>
<td>EU</td>
<td>AUC from 0 to last measurable point (AUClast)</td>
<td>AUClast should be more than 80% of AUCinf</td>
</tr>
<tr>
<td>US</td>
<td>AUClast or AUC from 0 to infinity (AUCinf)</td>
<td>Not defined</td>
</tr>
</tbody>
</table>

Table 1. Definition of AUC used for primary BE assessment in ICH countries

Received April 1, 2012; Accepted May 7, 2012
J-STAGE Advance Published Date: May 22, 2012, doi:10.2133/dmpk.DMPK-12-RG-033
*To whom correspondence should be addressed: Koji CHIBA, Ph.D., Department of Drug Development Science & Clinical Evaluation, Keio University Faculty of Pharmacy, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan. Tel. +81-3-5400-2649, Fax. +81-3-5400-2649, E-mail: chiba-kj@pha.keio.ac.jp
AUC\textsubscript{last}. If concentrations in terminal phase are below LLOQ (BLQ), AUC\textsubscript{all} includes an extrapolated area from the last measurable point to the next sampling point in BLQ which is set as zero. For immediate release (IR) formulation, the elimination phase after the time of peak concentration depends on the pharmacokinetic property of the active ingredient rather than the dissolution profile of a formulation. However, for sustained release (SR) formulation, the apparent elimination phase reflects the absorption profile which depends on a formulation. Different absorption profiles which are attributed to formulation difference can be measured as the difference of AUC. Therefore, the pivotal assessment of the extent of exposure using the appropriate AUC is vital especially for BE assessment of generic drugs in SR formulation.

We investigated how the difference in the definition of truncated AUC between Japan and the EU affects BE assessment of SR formulation.

**Methods**

The present analyses were composed of two processes: simulation and case examples in generic products currently available in the Japanese market. A simulation was carried out to investigate the possibility of different judgments in BE assessment based on the Japanese and EU AUC definition, i.e., AUC\textsubscript{all} and AUC\textsubscript{last}. Generic drug case examples in the current Japanese market provided a different conclusion on the validity of truncated AUC for BE assessment between the regional regulatory AUC definitions. The validity is defined as truncated AUC (AUC\textsubscript{all} or AUC\textsubscript{last})/AUC\textsubscript{inf} ≥80% in both BE regulations.

**Simulation:** The concentration-time profiles for SR formulation were simulated with flip-flop pharmacokinetics by convolution of 1st order dissolution terminated at 12 h or 24 h, and a 2-compartment model with 1st order absorption without lag time which is described as \[ A \exp(-\alpha t) + B \exp(-\beta t) - (A + B) \exp(-\kappa t) \] using R version 2.5.1. Kinetic parameters were set as follows: dissolution rate = 0.1 L/h, \( A = 17.5 \), \( B = 4 \), \( \alpha = 0.53 \text{ L/h} \), \( \beta = 0.16 \) and \( \kappa a = 0.92 \text{ L/h} \). The LLOQ was set as 1.5 ng/mL. Under the conditions provided, the ratio of theoretical AUC\textsubscript{infs} calculated using models for 12-h dissolution formulation to 24-h formulation was 0.77, which was less than 0.80.

**Fig. 2. Definition of truncated AUC used for BE assessment in Japan and the EU**

AUC\textsubscript{last} is used in the EU guideline. AUC\textsubscript{all}, which is the sum of AUC\textsubscript{last} and the extrapolated area from the last measurable point to the next sampling point in BLQ which is set as zero, is used in the Japanese guideline. In both regulations, AUC\textsubscript{last} or AUC\textsubscript{all} should be more than 80% of AUC\textsubscript{inf}.

**Table 2. The conditions to simulate the concentration-time profile of SR formulation**

<table>
<thead>
<tr>
<th>Case</th>
<th>Formulation</th>
<th>Blood sampling time</th>
<th>Time of the last measurable point</th>
<th>Time of the last sampling point</th>
<th>Lower limit of concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SR formulation with dissolution till 12 h</td>
<td>Predose, 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 24, 30 and 48 h</td>
<td>30 h</td>
<td></td>
<td>48 h 1.5 ng/mL</td>
</tr>
<tr>
<td>B</td>
<td>SR formulation with dissolution till 24 h</td>
<td>Predose, 1, 2, 3, 4, 5, 6, 8, 10, 11, 12 and 48 h</td>
<td>12 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>SR formulation with dissolution till 12 h</td>
<td>Predose, 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, and 48 h</td>
<td>12 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>SR formulation with dissolution till 24 h</td>
<td>Predose, 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, and 48 h</td>
<td>12 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case examples in Japanese generic drug package inserts: Case examples of different conclusions on the validity of truncated AUC for BE assessment based on AUCall and AUClast were identified in Japanese package inserts of currently commercially available generic drugs of SR formulation. A total of 39 products was selected from 112 products of which the name included “sustained” in Japanese i.e., “johousei” found on the homepage of Japanese package inserts on July 27th, 2011 by the following conditions: Concentration at the last sampling point in generic product’s data is to be BLQ. The BLQ at the last sampling point was decided when the concentration at the last sampling point in a graph of mean concentration-time profile was zero without error bars of standard deviation or standard error by observation. AUCall, AUClast and AUCinf were calculated by the linear trapezoidal rule using WinNonlin version 5.2 (Certara).

Results

Simulation: The simulation results are shown in Figure 3 and Table 3. When the sampling points were set to have ≥80% of AUClast/AUCinf, AUCall/AUCinf was also ≥80% (Figs. 3A and 3B and Table 3). However, if the sampling points were arranged to have the last measurable point equal to or before the end of dissolution and the next time point was set to have AUCall/AUCinf being ≥80%, AUClast/AUCinf could not be ≥80% (Figs. 3C and 3D and Table 3). In addition, if the sampling times were set to have ≥80% of AUClast/AUCinf, the geometric mean difference due to difference in the dissolution profile was detected as about 15% difference both in AUClast and AUCall.
AUCall (Table 3). In contrast, if the sampling time was arranged to have the last measurable point equal to or before the end of dissolution and the next time point was arranged to provide \( \geq 80\% \) of AUCall/AUCinf and <80% of AUClast/AUCinf, the ratio of geometric means of AUCall for 12-h formulation and 24-h formulation were measured as identical, \( i.e. \), the ratio was 1.

Case examples in Japanese package inserts: The search results on current Japanese package inserts of commercially available generic drugs in SR formulation is shown in Figure 4. In a total of 39 products investigated, there were 2 products\(^5,6\) among them for which AUCall/AUCinf of the test drug was \( \geq 80\% \) though AUClast/AUCinf was <80%, \( i.e. \), AUC was accepted using BE assessment based on Japanese criteria but was not accepted under EU criteria.

Discussion
In the current Japanese BE guideline, the truncated AUC which should be the primary endpoint is defined as “AUC from 0 to the last sampling time (\( t_\text{end} \))”. This definition could be read both as AUClast and AUCall. In the present study, we identified actual case examples which used AUCall as the truncated AUC to assess BE in Japanese package inserts. Therefore, at least for some cases, AUCall was used as the primary BE endpoint and got approval in Japan.

AUClast is determined only by the place of the last measurable point, which depends on LLOQ, but AUCall can be controlled by the distance between the last measurable point and the next sampling point when the next point is BLQ. This means that AUCall/AUCinf can intentionally be controlled by study design though AUClast/AUCinf cannot be. Our simulation result demonstrated that AUCall/AUCinf could be \( \geq 80\% \) despite the fact that AUClast/AUCinf was <80%. This result showed that the different judgment on the validity of truncated AUC for BE assessment could be led by using AUCall (Japan) and AUClast (EU), \( i.e. \), some study data are judged as appropriate data for BE assessment based on Japanese criteria, but are not accepted under EU criteria.

In addition to the difference of the judgment on validity of truncated AUC for BE assessment, the simulation result showed sensitivity to detect exposure difference caused by the different dissolution profile in SR formulations was different between AUCall and AUClast. In the simulation, when AUC of 2 SR formulations with different dissolution profiles which led to about 20% difference in the ratio of theoretical AUCinf, BE assessment based on AUClast could detect the difference as a 15% difference but AUCall failed to detect the difference. Both truncated AUCs satisfied the validity criteria (truncated AUC/AUCinf \( \geq 80\% \)). The ratio of AUCall was identical, \( i.e. \), the ratio was 1 if the last measurable point equaled or was before the dissolution end. This was because the extrapolated area between the last measurable point and the next sampling point in BLQ masked different concentration profiles reflecting different dissolution profiles. Even using AUClast, the true AUCinf difference of 20% could not be detected. However, if the ratio of geometric mean of the test product to the reference is 1.15, the sample size to demonstrate BE using AUClast with power = 80% is 144 in total under the assumption of coefficient of variances (CV) of geometric mean ratio being 20%.\(^7\) Even though it is not a highly variable drug\(^3\) which has less than 30% of CV, more than one hundred sample numbers requires a costly BE study. This could be one of the barriers to the entry of generic products in SR formulation with a substantially different dissolution profile compared to the original product in the market.

We had confirmed that a different conclusion on the validity of truncated AUC for BE assessment could be observed not only for SR formulation but also for IR formulation with the examples of approved generic drugs in Japan (data not shown). However, the formulation difference of IR formulation should appear in the absorption phase till around Tmax\(^8\) and the observed elimination phase reflects pharmacokinetic characteristics of the compound. One of the exceptions might be the case where the drugs have a non-linear elimination process in which the absorbed amount of the drug influences the elimination profiles, but it
must be quite a rare case. Therefore, the difference between AUCall and AUClast may not be a critical issue for BE assessment of IR formulation.

In the Japanese BE guideline, before conducting a human BE study, in vitro dissolution profiles should be confirmed and should meet the criteria of similarity. Therefore, it is unlikely that generic drugs with extremely different dissolution profiles from the original product will be marketed. However, more robust barriers for in vivo assessments using AUClast may be necessary to protect the patients and obtain reliability for generic drugs.

References