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Assessment of the impact of partial area under the curve in a bioavailability/bioequivalence study on generic prolonged-release formulations☆

Kelen Carine Costa Soares [a,*], Chang Chiann [b], Sílvia Storpirtis [c]

[a] Therapeutic Equivalence Coordenation, General Medicine Management, Brazilian Health Surveillance Agency, SIA trecho 05, Guará, Brasilia-DF, 71205-050, Brazil
[b] Statistics Department, Institute of Mathematics and Statistics, University of São Paulo, São Paulo, Brazil
[c] Pharmaceutical Research Institute Foundation (Fipfarma), Sao Paulo, Brazil

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ABSTRACT

The requirement for multiple-dose bioequivalence studies for the approval of generic prolonged-release (PR) formulations is not agreed upon by the EMA and FDA. While the EMA requests these studies, the FDA has no specific requirement, nor does ANVISA.

Additional metrics are suggested for the assessment of prolonged-release products, and the partial Area Under the Curve (pAUC) metric has received increasing regulatory recognition.

The objective of this work was to investigate whether the evaluation of the partial AUC in studies assessed by ANVISA can detect differences between 2 prolonged-release formulations that have demonstrated bioequivalence by the usual metrics.

Twenty-four studies in a total of 117, which were already approved by ANVISA considering the usual metrics in the last 14 years, failed to demonstrate bioequivalence for partial AUC, which is related to 33.9% of evaluated PR products.

For 76.92% of the studies, there was no significant increase in the intrasubject variability observed in the partial AUC analysis compared to the usual metrics, with a CV $< 30\%$ for both cases, calculated individually for each study, indicating that there is no need to increase the sample size to perform such analysis.

The results of this paper demonstrate that the current criteria for assessing the bioequivalence of some prolonged-release formulations are insufficient and that the evaluation of partial AUC could be useful to assure the therapeutic parity of two products.

1. Introduction

The requirement for multiple-dose bioequivalence studies for the approval of generic prolonged-release (PR) formulations is not agreed upon by the two main regulatory agencies of the world (Paixão, 2012). PR formulations, according to EMA guidelines, are modified-release formulations showing sustained release comparable to that of an immediate-release (IR) formulation administered by the same route. This deliberate modification is achieved by special formulation design and/or manufacturing methods. Additionally, according to the same guidelines, bioequivalence between two PR formulations should be evaluated based on studies designed to demonstrate that the test formulation exhibits the claimed PR characteristics of the reference (EMA, 2014).

In Europe, multiple-dose studies are mandatory for the determination of bioequivalence between innovator and generic PR formulations where accumulation is likely ($AUC_{0-\tau}$ after the first dose covers less than 90% of the mean $AUC_{0-\infty}$) (EMA, 2014). When a low extent of accumulation is expected, bioequivalence needs to be demonstrated for additional parameters representing the shape of the plasma concentration versus time curve in a single-dose study, such as an initial partial Area Under the Curve (pAUC) and a terminal pAUC separated by a predefined time point, which is usually half of the dosage interval (EMA, 2014). On the other hand, the US-FDA does not have these requisites, and there is no special difference between the requirements for a generic IR formulation and a generic PR formulation (Endrenyi and

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* Corresponding author.
E-mail addresses: kelen.soares@anvisa.gov.br (K.C.C. Soares), chang@ime.usp.br (C. Chiann).

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Tothfalusi, 2012), except for some modified-release products with complex PK profiles and for products in which different phases of release corresponds to a clinical effect (FDA, 2010, 2011, 2018a, 2018b). However, some papers raised questions regarding whether the primary metrics (AUC_{0-t} and Cmax) for determining the BE are sufficient in a class of modified-release products (FDA, 2010; lionberger et al., 2012).

In Brazil, as recommended by the US-FDA, there is not currently a specific requisite for generic PR products (ANVISA, 2006; FDA, 2003); however, considering that the shape of plasma profiles for a PR product is much more dependent on the formulation than that of plasma profiles for an IR product (Garcia-Arieta et al., 2012), a discussion on the need to evaluate other parameters, differing from those used for IR products (Cmax and AUC_{0-t}), has started with the revision process of the RE 1170 /2006 standard.

PR formulations are developed to release the drug more slowly than the IR product and typically yield a long concentration plateau period. The release mechanisms of the reference and generic product may vary, but the generic product should have a rate, a time course, and an extent of absorption equivalent to those of the reference product. Inappropriate control of drug release from such products may result in reduced efficacy or increased toxicity (Chen et al., 2010).

Additional metrics, such as the pAUC, the ratio of Cmax to AUC_{0-t}, the area under the moment curve (AUMC), the apical concentration (Capical) and the concentration at the end of the intended dosing interval (Cτ), are suggested for the assessment of modified-release products (Endrenyi and Tothfalusi, 2012). The pAUC metric has found increasing regulatory recognition. The drafted FDA guidelines on the bioequivalence of extended-release tablets of zolpidem tartrate and methylphenidate recommend that 90% confidence intervals for the ratio of geometric means should be established not only for AUC_{0-t} and Cmax but also for pAUCs (FDA, 2011, 2018a).

In this context, the purpose of this paper was to identify whether the evaluation of the pAUC for generic and similar PR products assessed in the last 14 years for registration in Brazil can demonstrate differences that were not identified with the usual parameters.

2. Material and methods

All PR generic and similar products (regardless of pharmaceutical dosage form) assessed in Brazil by ANVISA since 2008 that were available on SINEB, an ANVISA internal system that started to be used in this year, were included in this investigation. Among the investigated studies, only studies approved by ANVISA considering the usual parameters for bioequivalence (Cmax and AUC_{0-t}) were collected and reviewed. Pilot studies were not considered.

The term generic product is widely used for pharmaceutical products with recognized intellectual property rights, whereas the term similar is more specific to Brazil for products where no patent protection rights exist, at least for a period of time (Storpirtis et al., 2014).

3. Results

A total of 117 studies were collected that referred to the registration of 59 different products (58 oral products and one transdermal product). This difference between the number of studies and the number of products is because for each PR product, it is necessary to present two studies, considering fed and fasting states. This two-study requirement is not the case for a transdermal patch, for which only a fasting study is required for registration in Brazil (ANVISA, 2006).

Considering all 117 studies, the initial pAUC and the terminal pAUC were calculated considering half of the dosage interval for each product (EMA, 2014), which is described in the package insert of the reference product. For products where more than one dosing schedule was noted, both dosage intervals were considered.

A total of 24 studies failed to demonstrate bioequivalence for initial pAUC or terminal pAUC or both, with a 90% CI outside the acceptance range (80.00–125.00%). This number of failed studies referred to a total of 20 products (33.9% of evaluated products). The results found considering the failed studies are shown in Table 1.

As seen in Table 1, deviation out of the acceptance range was shown by 10 studies for the initial pAUC, 12 studies for the terminal pAUC and two studies for both pAUCs. In addition, within the 24 studies outside the acceptance range, 18 studies showed a result totally displaced from 100%, which may demonstrate that the problem is indeed in the product and not a result of study's variability. For drugs 3 and 9, all products failed at the initial pAUC, and for drugs 4 and 7, all the products failed at the terminal pAUC. For drug 4, the FDA has guidance that mentions the need to assess the pAUC (FDA, 2018b).

Nine of the 24 studies (the highlighted ones) point out that the two portions of the pAUC are completely different, with no point of convergence, indicating that the test drug behaves completely differently from the reference, and in some cases, the test drug is less absorbed than the reference at the beginning and much more absorbed in the final portion (studies 4, 13, 17, 20 and 21) and vice versa (studies 8, 9, 23 and 24). Although some products met the acceptance criteria of the 80 to 125% acceptance limit for the pAUC, their behavior was quite different from that of the reference considering the two portions of the curve (initial and terminal pAUCs).

Considering this observation, whether the test formulation behaves as a PR formulation was considered, since the initial release profile of the test was sometimes much larger than that of the reference and the final profile was smaller, which may indicate that most of the drug in the test formulation was initially released, unlike that in the reference product. In contrast, a greater release of the test product compared to that of the reference in the final portion of the curve and a lesser release in the first portion were also observed, but in both situations, the drug did not undergo the continuous release shown by the reference. To verify how many formulations, among the registered formulations, present this behavior, the two portions of the pAUC, initial pAUC and terminal pAUC were compared. For this, the ratio of the initial pAUCs of the test and reference products was calculated, with the same being done for the terminal pAUC, and the ratios were compared. The statistical method used to perform this assessment is the same bioequivalence method used for the 2 × 2 crossover study, where the individual values of $\ln(AUC_{0-t}$ of the test formulation) and $\ln(AUC_{0-t}$ of the reference formulation) are replaced by (ln(initial pAUC of the test formulation) - ln(terminal pAUC of the test formulation)) and (ln(initial pAUC of the reference formulation) -ln(terminal pAUC of the reference formulation)), respectively.

Of the 117 studies, 36 presented 90% CIs for the initial pAUC T/R versus terminal pAUC T/R outside the acceptance range of 80.00–125.00%, which represents 24 (41%) products (Table 2). Of these 36 studies, 19 also presented 90% CI outside the acceptance range for initial pAUC or terminal pAUC, and the other 17 met the acceptance criteria for each portion (initial or terminal); however, the difference between the two portions of the pAUC was outside the acceptance range.

A concern regarding the pAUC evaluation is the possible need to increase the number of volunteers (N) to correctly evaluate this parameter. To assess whether the analysis of pAUC has an impact on N, the intraindividual variation coefficients of pAUC from all 117 studies were evaluated. Studies with a CV > 30% may indicate that a higher N, more than that used considering the primary parameters, would be necessary to assess pAUC.

A total of 90 studies (76.92%) presented a CV ⟨ 30%. Of the 27 studies that presented a CV ⟩ 30%, 13 (48.2%) were approved (90% CI within the acceptance range). Additionally, considering the 24 studies that failed the assessment of pAUC, 10 studies (41.67%) had a CV <30%. These results indicate that these failures were not due to excessive variability in the analysis of pAUC. However, it seems that differences between formulations exist, either in the early-onset responses or in the maintenance responses, and these differences were not detected with usual metrics.

Table 1
Studies that failed to demonstrate bioequivalence for initial pAUC, terminal p AUC or both.

STUDY	Drug	AUC 0-t	Initial pAUC	Terminal pAUC
1	1	84.20–100.62%	90.80–109.43%	**79.63–98.89%**
2	2	91.47–97.82%	108.03–114.76%	**76.31–84.71%**
3	3*	103.20–112.35%	**t1: 76.26–100.84%** t2: 92.35–106.02%	t1: 105.59–115.85% t2: 105.97–117.96%
4	3*	100.08–109.99%	**t1: 66.43–94.33% t2: 75.65–102.38%**	t1: 104.58–116.73% t2: 106.41–120.74%
5	3*	90.94–101.32%	**t1: 73.24–83.01%** t2: 81.50 −91.03%	t1: 96.05–108.34% t2: 95.54–109.16%
6	3*	93.31–103.20%	**t1: 74.76–123.97%** t2: 86.38–109.20%	t1: 95.17–107.38% t2: 94.13–109.80%
7	3*	100.78–109.95%	**t1: 115.80–148.66%** t2: 97.80–112.48%	t1: 97.62–106.53% t2: 97.22–106.46%
8	3*	98.21–108.63%	**t1: 179.25–330.19% t2: 130.30–166.00%**	t1: 94.81–105.81% t2: 89.39–100.58%
9	3*	92.35–114.56%	**t1: 152.75–253.49% t2: 113.79–138.69%**	**t1: 90.59–113.70% t2: 87.81–138.66%**
10	3*	102.28 – 109.50%	**t1: 70.02–110.,91% t2: 104.62–125.49%**	t1: 102.43–110.27% t2: 101.03–108.71%
11	4*	89.42–101.19%	t1: 85.81–99.12% t2: 95.18–107.55%	t1: 89.01–105.77% **t2: 66.65–88.01%**
12	4*	88.42–97.46%	t1: 86.30–109.65% t2: 95.51–104.65%	t1:84.11–97.70% **t2:67.49–87.37%**
13	4*	96.71–107.78%	t1: 85.74–95.08% t2: 91.86–101.28%	t1: 103.26–119.74% **t2: 107.11–131.19%**
14	5	85.58–99.33%	87.24–100.53%	**79.75–91.30%**
15	5	94.33 – 118.90%	**97.07–140.66%**	91.15–116.98%
16	6**	Drug A: 96.86–108.45% Drug B: 102.49–115.57%	Drug A: 96.11–104.14% Drug B: 99.66–108.90%	Drug A: 94.10–113.70% Drug B: **104.20–129.52%**
17	7	97.93–109.36%	89.10–101.70%	**107.09–127.43%**
18	7	88.60–102.32%	92.76–106.09%	**76.42–101.98%**
19	8	81.74–103.12%	84.93–96.17%	**77.06–108.77%**
20	9*	93.57–100.66%	**t1: 34.34–38.49% t2: 59.97–65.28%**	t1: 103.59–111.49% **t2: 117.42–127.41%**
21	9*	100.89–108.06%	**t1: 58.16–68.52%** t2: 93.84–105.52%	t1: 108.53–116.41% t2: 100.22 – 110.74%
22	10	100.00–115.57%	96.92–110.41%	**98.21–125.74%**
23	11	104.67–114.74%	**113.29 −125.43%**	93.31–106.28%
24	11	90.86–105.26%	104.98–115.36%	**79.44–97.17%**

* Drugs with two different dosage intervals.
** Products with more than one drug.

Table 2
Studies with the initial pAUC T/R versus terminal pAUC T/R outside the acceptance range.

STUDY	DRUG	Initial pAUC T/R	Terminal pAUC T/R	Initial vs terminal pAUC T/R
2	Drug 02	108.03 −114.76%	**76.31–84.71%**	131.70–145.63%
25	Drug 02	100.10 −109.54%	80.20–89.95%	115.54–131.56%
26	Drug 02	103.13 −110.54%	80.78–93.09%	114.89–131.94%
3	Drug 03*	**t1:76.26 −100.84%** t2: 92.35 −106.02%	t1:105.59–115.85% t2:105.97–117.96%	t1: 68.40–91.91% t2: 81.44–96.18%
4	Drug 03*	**t1: 66.43–94.33% t2:75.65 −102.38%**	t1: 104.58–116.73% t2: 106.41–120.74%	t1: 59.23–86.67% t2: 65.21–92.44%
5	Drug 03*	**t1: 73.24–83.01%** t2: 81.54–91.03%	t1: 96.05–108.34% t2: 95.54–109.16%	t1: 72.07–81.49% t2: 79.68–89.61%
6	Drug 03*	**t1: 74.76–123.97%** t2: 86.38–109.2%	t1: 95.17–107.38% t2: 94.13–109.80%	t1: 71.57–126.71% t2: 80.62–113.18%
7	Drug 03*	**t1: 115.80–148.66%** t2: 97.80–112.48%	t1: 97.62–106.53% t2: 97.22–106.46%	t1: 114.29–144.84% t2: 96.42–110.23%
8	Drug 03*	**t1: 179.25–330.19% t2: 130.30–166.00%**	t1: 94.81–105.81% t2: 89.39–100.58%	t1: 177.76–366.07% t2: 135.94–176.97%
27	Drug 03*	t1: 84.02–123.66% t2: 89.34–105.10%	t1: 90.58–105.44% t2: 89.23–104.62%	t1: 83.91–129.34% t2: 91.13–110.06%
09	Drug 03*	**t1: 152.75–253.49%** t2: 113.79–138.69%	t1: 90.59–113.70% **t2: 87.81–138.66%**	t1: 144.68–259.59% t2: 110.81–144.98%
10	Drug 03*	**t1: 70.02–110.91% t2: 104.62–125.49%**	t1: 102.43–110.27% t2: 101.03–108.71%	t1: 65.02–105.75% t2: 98.97–120.52%
28	Drug 03*	t1: 100.38–115.58% t2: 96.18–108.16%	t1: 83.97–96.55% t2: 83.43–97.49%	t1: 110.28–129.77% t2: 105.45–121.29%
29	Drug 03*	t1: 101.90–124.46% t2: 100.87–110.82%	t1: 84.05–95.97% t2: 81.18–93.88%	t1: 109.69–143.33% t2: 112.31–130.59%
30	Drug 03*	t1: 83.63–101.54% t2: 93.40–103.59%	t1: 99.97–110.73% t2: 101.13–112.89%	t1: 77.45–99.04% t2: 86.41–98.08%
11	Drug 04*	t1: 85.81–99.12% t2: 95.18–107.55%	t1: 89.01–105.77% **t2: 66.65–88.01%**	t1: 85.94–105.12% t2: 115.54–151.04%
12	Drug 04*	t1: 86.30–109.65% t2: 95.51–104.65%	t1: 84.11–97.70% **t2: 67.49–87.37%**	t1: 92.21–124.88% t2: 114.82–147.63%
13	Drug 04*	t1: 85.74–95.08% t2: 91.86–101.28%	t1: 103.26–119.74 **t2: 107.11 – 131.19**	t1: 75.32–87.,53% t2: 74.38–89.01%
31	Drug 04*	t1: 81.34–90.5% t2: 92.79–100.72%	t1: 104.39–121.66% t2: 99.58–118.40%	t1: 69.44–83.33% t2: 81.93–95.65%
15		**97.07–140.66%**	91.15–116.98%	89.84–132.63%

(*continued on next page*)

Table 2 (*continued*)

STUDY	DRUG	Initial pAUC T/R	Terminal pAUC T/R	Initial vs terminal pAUC T/R
	Drug 05			
32	Drug 12	82.84–104.94%	97.93–104.99%	78.6–105.18%
33	Drug 13	81.36–89.57%	100.04–108.42%	76.66–87.65%
17	Drug 07	89.10–101.70%	**107.09–127.43%**	73.24–90.66%
34	Drug 07	104.53–119.96%	90.98–109.18%	99.95–126.30%
18	Drug 07	92.76–106.09%	**76.42–101.98%**	97.78–129.14%
20	Drug 09*	**t1: 34.34–38.49% t2: 59.97–65.28%**	t1:103.59–111.49% **t2: 117.42–127.41%**	t1: 32.22–35.53% t2: 49.23–53.15%
21	Drug 09*	**t1: 58.16–68.52%** t2: 93.84–105.52%	t1: 108.53–116.41% t2: 100.22–110.74%	t1: 51.75–60.95% t2: 87.08–102.46%
35	Drug 14**	Drug A: 86.83–94.49%	Drug A: 104.88–118.28%	Drug A: 76.49–89.46%
36	Drug 14**	Drug A: 106.56–117.18% Drug B: 92.44–102.06%	Drug A: 84.25–98.69% Drug B: 91.86–102.36%	Drug A: 114.92–130.68% Drug B: 94.25–106.46%
37	Drug 10	83.66–98.07%	99.64–119.18%	74.97–92.15%
38	Drug 11	90.06–98.50%	108.28–124.85%	76.63–85.63%
39	Drug 11	108.31–119.86%	86.08–99.76%	115.63–130.74%
23	Drug 11	**113.29–125.43%**	93.31–106.28%	111.49–128.51%
40	Drug 11	98.46–106.81%	81.41–102.72%	100.24–125.47%
24	Drug 11	104.98–115.36%	**79.44–97.17%**	116.48–134.67%
41	Drug 11	104.28–116.18%	86.89–103.41%	108.93–128.32%

* Drugs with two different dosage intervals.
** Products with more than one drug, quantifying in study 35 only one of the drugs (a) and in study 36 both drugs in combination (*A* + B*)*.

4. Discussion(Anschütz et al., 2010; ANVISA, 2006, EMA, 2014, FDA, 2011, FDA, 2018a, FDA, 2018b; Chen et al., 2010; Endrenyi and Tothfalusi, 2010, 2012; Garcia-Arieta et al., 2012; Gonzalez et al., 2020; Lionberger et al., 2012; Midha et al., 2005; Paixão et al., 2012; Storpirtis et al., 2014; FDA 2003; FDA 2010)

According to the EMA guidelines (EMA, 2014), the establishment of bioequivalence between PR products should be made based on single- and multiple-dose studies that are designed to demonstrate the same claimed PR characteristics for the test product as the reference product with equivalent performance (Paixão et al., 2012).

The FDA makes a statement similar to that used for IR formulations, for which multiple-dose studies are generally not accepted, since they are less able to detect differences between formulations in Cmax (FDA, 2003).

The use of pAUC has been recently considered to assess the BE of some PR formulations. For instance, in studies on methylphenidate (Gonzalez et al., 2020), nifedipine (Anschütz et al., 2010) and bupropion (Midha et al., 2005) modified-release products, traditional regulatory criteria found two formulations to be bioequivalent even though they have conspicuously different concentration profile shapes (Endrenyi and Tothfalusi, 2012).

Of the 117 studies on PR formulations already approved by ANVISA, a total of 24 (20%) failed to demonstrate bioequivalence for the pAUC parameter. For one drug (an opioid) that is the subject of three of these 24 studies, the FDA has a recommendation for pAUC, which is based on exposure-response relationships, but regardless of the pharmacological class and possible adverse events or lack of efficacy that the dissimilar pAUC may represent, interchangeable products must release the drug at the same rate and extent as the reference product. Since the shape of the plasma profiles of a PR product is much more dependent on the formulation than that of the plasma profiles of an IR product (Garcia-Arieta et al., 2012), the evaluation of the plasma profile of PR products seems to deserve more attention than that of IR products. That the plasma profile of PR products deserves more attention than that of IR products verifies that the parameters commonly used to define the bioequivalence of IR products are not sufficient for PR products.

Considering the 24 studies that failed to demonstrate bioequivalence using the pAUC parameter, it was noted that the 90% CI obtained for the initial pAUC was very different from that obtained for the terminal pAUC, which may indicate that the products do not behave the same way over the dosage interval but that this difference can be masked by the assessment of $AUC_{0\text{-}t}$, a parameter currently used, which can be clinically significant in some cases.

Fig. 1 illustrates the results obtained for drug 2 from study 2. It is an example where the initial pAUC does not converge with the terminal pAUC at any point, and the difference between the products is masked by the average AUC (AUC0-t).

Considering this difference between the two portions of the pAUC, the 90% CI of initial pAUC T/R versus terminal pAUC T/R was calculated, and 36 out of a total of 117 studies evaluated showed results outside the acceptance criteria of 80.00–125.00% (Table 2). Such an observation indicates that for many products already registered in Brazil, the release of the test drug does not behave in the same way as that of the reference drug (that is, the formulation is able to release more drug in the initial portion and less drug in the end times or vice versa), yet products are considered the same when only the mean ($ASC_{0\text{-}t}$) is evaluated. An example of this can be seen in Fig. 2, which illustrates the time courses of average concentrations after drug 2 administration in a single-dose study (study 2). Both the peak concentrations and AUCs of the two formulations appear to be comparable. However, the shapes of the concentration profiles are quite different.

Since differences in the shape of the plasma profile may be of high clinical relevance and this difference observed between the test and reference is seen only with the pAUC, this kind of analysis cannot be ignored if a multiple-dose study is not a requirement.

Intrasubject variability observed with the pAUC analysis was investigated since it can increase the number of subjects needed in studies to achieve sufficient power to demonstrate the similarity between two formulations.

Evaluation of the variation coefficient performed to verify whether a larger number of volunteers would be necessary in a study, in addition to what is already considered, demonstrated that the N used for the vast majority of studies (76.92%) is sufficient to evaluate the pAUC, with no need to change the protocols of the studies that are already being done to register a generic PR product.

In addition, considering the studies that presented a CV > 30%, half were approved (90% CI within the acceptance range), which is a strong indication that it is not necessary to increase N to evaluate the pAUC.

Additionally, considering the 36 studies that presented CIs outside the acceptance range in the evaluation of the initial pAUC T/R versus the final pAUC T/R, 23 (64%) presented low CVs, indicating that N does not influence the analysis of the plasma profile formulations.

5. Conclusions

It is possible that two PR products satisfy the bioequivalence criteria, showing similarity according to usual pharmacokinetic parameters ($AUC_{0\text{-}t}$ and Cmax) even though their plasma profiles are different. This was the case for 20 PR products already registered in Brazil.

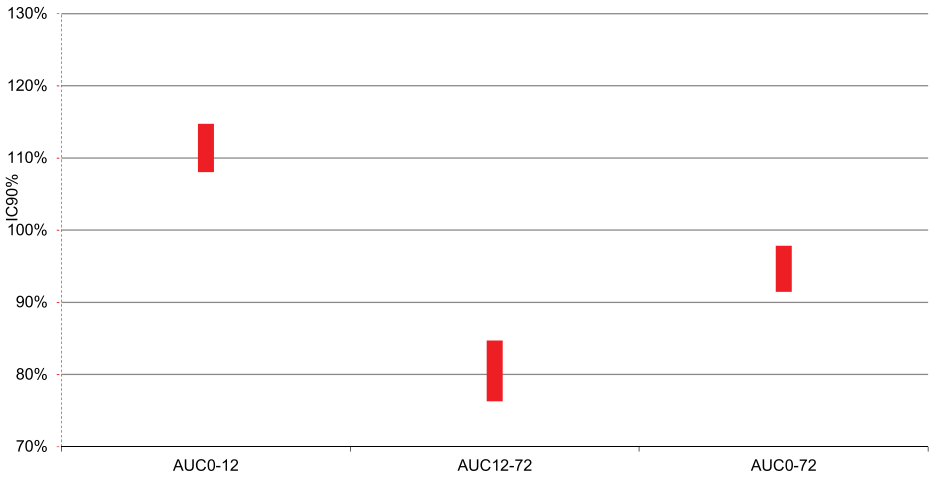

Figure 1 – An example that the bioequivalence based on the current two metrics does not guarantee therapeutic equivalence for PR products.

Fig. 1. An example that the bioequivalence based on the current two metrics does not guarantee therapeutic equivalence for PR products.

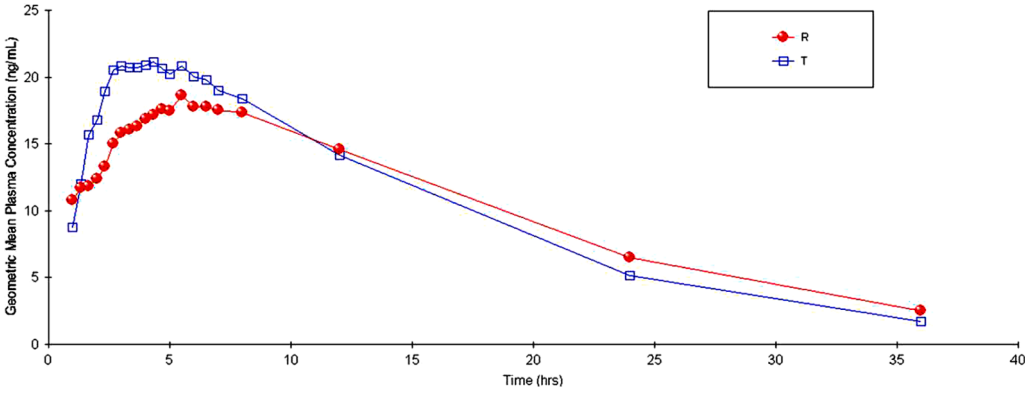

Fig. 2. the time courses of average concentrations after the drug 2 administration of a single-dose study.

The evaluations carried out with the studies already approved by ANVISA demonstrate that the current criteria for assessing the bioequivalence of some PR products can be insufficient, and it is necessary to evaluate the pAUC if a multiple-dose study is not required to assure the therapeutic parity of the two products.

In addition, the need to increase the N of the study that is already conducted at the time of registration to include the evaluation of pAUC has not been demonstrated. Therefore, any modification of the sample size in the study protocol is not necessary to perform this assessment, which can help in detecting differences between PR products when differences are masked by traditional analysis considering only $AUC_{0\text{-}t}$.

Because the harmonization of topics dealing with bioequivalence studies on modified release products (carried out by the ICH Group M13, of which ANVISA is part of) is expected to start only after June 2022, the differences found in the pAUC evaluation of registered products considering only the parameters $ASC_{0\text{-}t}$ and Cmax can help in the discussion of which parameters should be adopted to properly evaluate these products.

CRediT authorship contribution statement

Kelen Carine Costa Soares: Conceptualization, Validation, Formal analysis, Investigation, Resources, Writing – original draft. **Chang Chiann:** Methodology, Software, Investigation, Writing – review & editing, Visualization. **Sílvia Storpirtis:** Data curation, Writing – review & editing, Supervision.

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