Defining level A IVIVC dissolution specifications based on individual in vitro dissolution profiles of a controlled release formulation

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BACKGROUND

Regulatory guidelines recommend that, when a level A IVIVC is established, dissolution specification should be established using averaged data and the maximum difference between AUC and C_{max} between the reference and test formulations cannot be greater than 20%. However, averaging data assumes a loss of information and may reflect a bias in the results.

OBJECTIVES

The purpose of this work is to compare the classical approach (the use of mean data) with a new methodology in which we have used individual data in order to assess the probability of declaring bioequivalence for a new batch based on an IVIVC. Furthermore, we have evaluated the impact of these two different methodologies on the establishment of dissolution specifications.

METHODS

Figure 1 represents the workflow developed. A slow, medium and fast dissolving drug formulations were used to develop the IVIVC. Dissolution data sets were generated for 12 units (e.g. tablets) based on a first-order dissolution model and forced to show a similarity factor (f_2) below 50 between the medium and fast/slow formulation. A level A IVIVC using differential equations[1] was established using these three drug formulations, where the link between in vitro and in vivo performance of the drug products was related between in vitro and in vivo dissolution rate coefficients (k_d). Two types of scenarios were drawn:

- Linear relationship between $k_{d,\ in\ vitro}$ and $k_{d,\ in\ vivo}$ (Scenarios 1, 2, 3)
- Non-linear relationship between $k_{d,\ in\ vitro}$ and $k_{d,\ in\ vivo}$ (Scenarios 4, 5, 6)

Plasma profiles were generated using a one compartment model with first order dissolution, absorption, and elimination kinetics. Twelve individual units were considered for each formulation or batch. Batch suitability was assessed using six additional batches (12 units each). For each batch, simulation (n = 1,000) of a dissolution assay with 12 units was generated through Monte Carlo simulation approach. The percentage of BE batches was computed for each approach. BE of a new batch was concluded when the C_{max} ratio between reference and new batch formulations was within ±20%. Dissolution specifications were established as follows: (i) classical approach, in vitro dissolution limits of each formulation were computed using the batch whose ratio was the closest to ±20%; (ii) individual approach, the slowest tablet of the slowest dissolving formulation (STSF) or the fastest tablet of the fastest dissolving formulation (FTFF) whose ratio was exactly ±20%. The simulations were performed in NONMEM 7.3[2]. Graphical and statistical analysis were performed using R software and RStudio®.

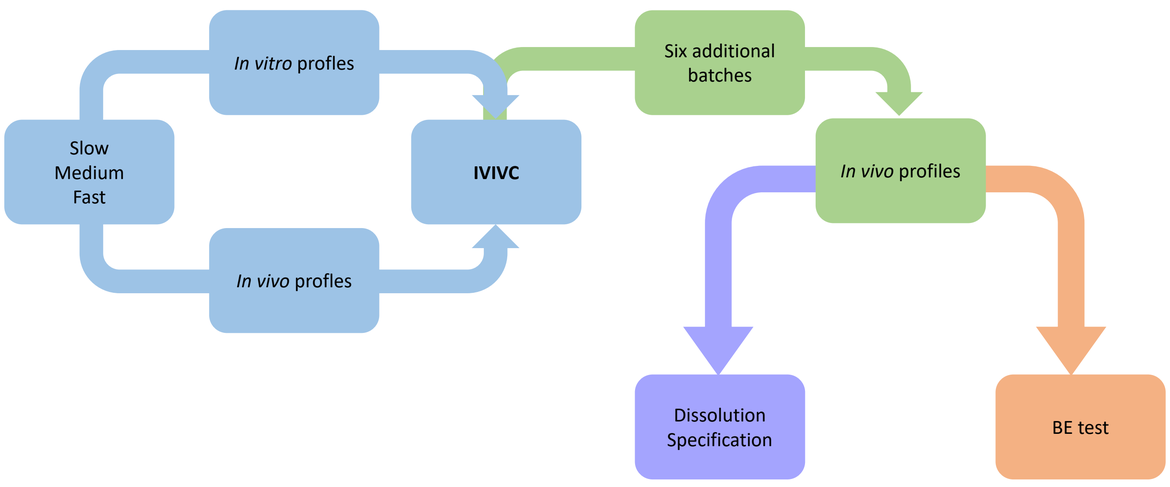

Figure 1. Workflow.

RESULTS

Plasma concentrations were calculated using the in vitro dissolved fraction and according to the linear (Scenarios 1-3) or non-linear (Scenarios 4-6) IVIVC link model. **Figure 2** represents the mean in vivo profiles for each type of formulation included in the development of the IVIVC. **Figure 3** represents the mean in vivo PK profile obtained from the mean in vitro dissolution profile for the reference formulation and the six batches considered.

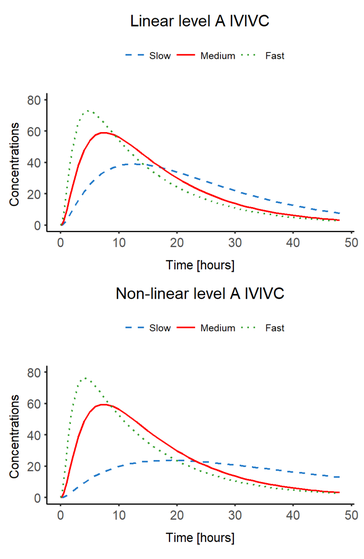

Figure 2. Plasma in vivo profiles obtained through IVIVC link (top linear IVIVC, bottom non-linear IVIVC)

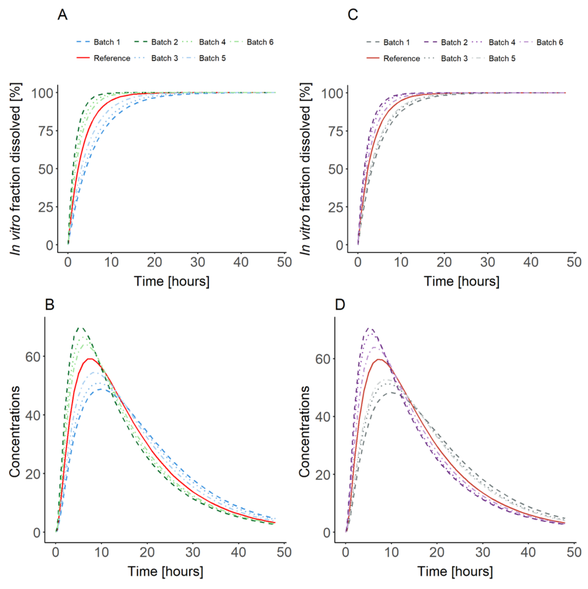

Figure 3. . Mean in vitro (top) and in vivo (bottom) profiles of the new batches (left linear scenarios, right non-linear scenarios).

According to the results from the classical approach (**Table 1** and **Figure 4**), the C_{max} ratio from the six batches fulfill the ±20% range under linear level A IVIVC. Similar results were observed for Batches 2-6 when non-linear level A IVIVC was developed, but only 78.6% of the simulations with Batch 1 achieved a C_{max} ratio within the ±20% difference. However, when the individual approach was applied under linear level A IVIVC, a significant amount of simulations with Batches 1 and 2 were out of ±20% limits: 53.3 and 58.1%, respectively. Greater differences between classical and individual approaches were observed for the non-linear relationship (scenarios 4-6), where the suitable number of batches of Batch 1 and 2 diminished to 0.3 and 15.5%, respectively. Additionally, 23.1% of the simulations with Batch 3 resulted in a C_{max} ratio greater than ±20% compared to the reference formulation. The dissolution performance of Batch 3 was more similar to the reference formulation than Batches 1 and 2, but differences were not detected when the classical approach was applied.

	C_{max} Ratios	
	Linear level A IVIVC	Non-linear level A IVIVC
Batch 1 / Reference formulation	82.6%	80.8%
Batch 2 / Reference formulation	118%	118%
Batch 3 / Reference formulation	86.1%	86.0%
Batch 4 / Reference formulation	113%	115%
Batch 5 / Reference formulation	92.0%	88.4%
Batch 6 / Reference formulation	108%	107%

Table 1. Cmax ratios obtained between the reference formulation used in the development of a level A IVIVC and the six new batches simulated (Batch 1-6).

The batches that were closest to ±20% difference on C_{max} (Batches 1 and 2) were used to establish the dissolution limit specifications (**Table 2**). The classical approach provides narrower specification limits because it is established based on the mean in vitro dissolution profile that is closest to ±20%, whereas the individual approach provides the dissolution specification limits that exactly achieved ±20% difference on C_{max} between reference and new batch.

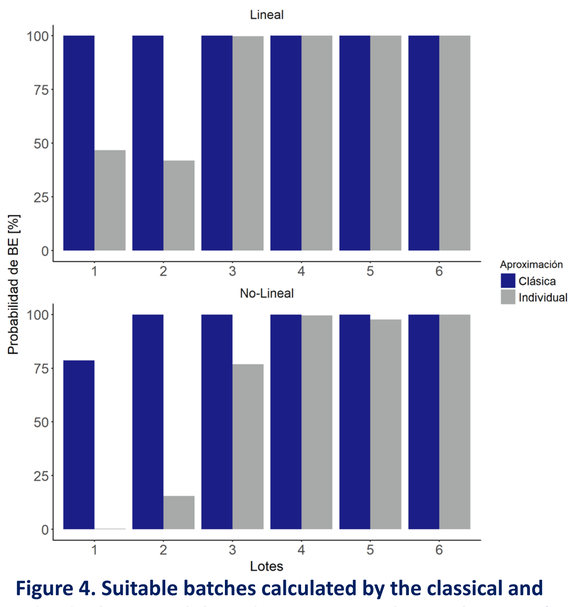

Figure 4. Suitable batches calculated by the classical and individual approach based on Monte Carlo simulations of a cross-over BE study (n=1,000).

Dissolved [%]	Classical approach [min]	Individual approach [min]
	Linear level A IVIVC	
25	30 – 120	30 – 120
50	75 – 270	60 – 300
85	165 – 780	165 – 840
	Non-linear level A IVIVC	
25	30 – 90	30 – 90
50	90 – 210	75 – 225
85	210 - 600	195 - 600

Table 2. Dissolution specifications for the different methodologies

The widening of the dissolution specification limits could be accomplished because individual data is used instead of average data. The use of the classical approach, which assumes a maximal difference of 20% in the predicted AUC and C_{max} using average data, might result in considering non-BE units within the batch as BE. Averaging data implies loss of information and use of the arithmetic mean might not be an adequate approach due to extreme For these reasons, this new approach makes use of the individual data to ensure BE for all tablets. The current constraint regarding the use of average data in the establishment of dissolution specifications has been highlighted in this analysis (**Figure 4**), showing the regulatory and clinical implications of declaring BE batches that contain non-BE units.

CONCLUSION

An individual approach has been proposed to establish the dissolution specifications using a level A IVIVC, ensuring BE of all units within the new batch developed. This methodology takes into consideration the in vitro and in vivo variability observed, providing the dissolution specification limits that ensure in vivo ratios exactly to 80-125. Thus, the widening of dissolution specification is a consequence of using individual data, but ensures the BE of all tablets, which is not always achieved using the classical approach.

References

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