Three methods of change-point definition were evaluated:

**Change-point methods using MTIME (MTIME\_meth)**
- the reference method, using model event time parameter (MTIME) directly implemented in NONMEM, MTIME parameter defines a time at which the system is updated.
- Adapted to NONMEM subroutines

**Change-point methods using a dummy compartment (CMT\_meth)**
- the use of a fictive change point compartment (CMT) with an associated lag time [1];

**Change-point method using a function (FCT\_meth)**
- A change point function (FCT) with an analytical expression of a rectangular wave function.

Each method was evaluated with a simulated population PK example: a 1 compartment model with a changing first-order absorption rate. Simulations were performed after **single administration (SD)**, **repeated doses (RD)** and at **steady state (SS)** and the simulated median profile were plotted. Graphical comparison and run time duration were used to evaluate each method. Practical constraints in terms of coding and/or data preparation were also discussed.

### Results

After single administration, the three methods give the same expected results. After multiple administrations, no difference in term of simulation output is observed between the three methods. As the reference method MTIME\_meth allows the use of an adapted NONMEM subroutine, run duration is shorter than CMT\_meth and FCT\_meth, which require using differential equations. At steady state (using the implemented NONMEM SS option) only the FCT\_meth is able to give the correct simulation results. From a practical point of view, MTIME\_meth involves heavy code adjustment and CMT\_meth requires specific dataset modification, while FCT\_meth can be used without significant modifications of both code and dataset.

### Conclusions

In order to implement a change-point model after a single dose administration, the **MTIME\_meth** was the easiest way to do it, allowing to the modeller to use NONMEM subroutines. For multiple dosing, the **CMT\_meth** and **FCT\_meth** are good alternatives when the number of doses increases. However, only the **FCT\_meth** is able to perform correct simulation at steady state using NONMEM SS option.