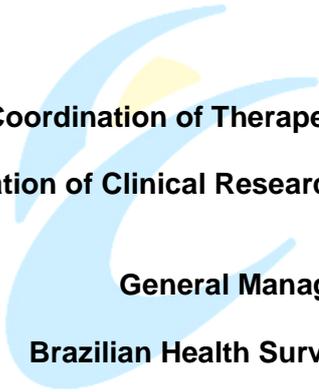


**TECHNICAL NOTE 118/2016**

**Clarifications on comparative pharmacokinetic studies of Biological Products**

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**Coordination of Therapeutic Equivalence - CETER**

**Coordination of Clinical Research in Drugs and Biological Products - COPEC**

**General Management of Drugs - GGMED**

**Brazilian Health Surveillance Agency - ANVISA**

**ABRACRO**

**Brasília, April 15, 2016.**

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**TECHNICAL NOTE No. 118/2016/GGMED/ANVISA- Health Ministry (MS)**

**Purpose: Comparative pharmacokinetic Studies of Biological Products (Biosimilar)**

1. With the purpose of defining, harmonizing, and accelerating procedures related to pharmacokinetic studies analysis of biological products developed through comparability, we explain that at the time of submitting clinical development dossiers for these drugs (DDCM), which contain completed pharmacokinetics clinical trials to support the proposed posterior phases, a secondary application should be submitted to Anvisa simultaneously to the DDCM with the subject code: 10900 – CLINICAL TRIALS – Comparative pharmacokinetic studies for experimental drugs – Biosimilar – submitted as DDCM.
2. The pharmacokinetics/pharmacodynamics clinical trials will have the evaluation by Clinical Research Coordination on Drug and Biological Products (COPEC) for the parameters and results of the phase I clinical trials, in pharmacodynamics terms, and by Coordination of Therapeutic Equivalence (CETER), in pharmacokinetics terms. Thus, there might be both requirement from COPEC and CETER relative to the Phase 1 clinical trial.
3. The pharmacokinetics clinical trial should be submitted to COPEC as part of the drug clinical development plan and to CETER through the secondary application to be linked to the DDCM process: 10900 – CLINICAL TRIALS – Comparative pharmacokinetic studies for experimental drugs – Biosimilar – submitted as DDCM.
4. In cases of analysis prioritization, COPEC and CETER will provide the first manifestation about the DDCM within up to 45 days after publication of the prioritization request approval. In cases where the prioritization is granted, but the applicant has not submitted the secondary application to CETER yet, this period of 45 days will be counted from the application submission: 10900 – CLINICAL TRIALS – Comparative pharmacokinetic studies for experimental drugs – Biosimilar – submitted as DDCM.
5. DDCM analysis cannot be completed without the final opinion of the pharmacokinetics parameters evaluation by CETER. This is important because similar pharmacokinetics profiles among biological products, when correlated to clinical safety and efficacy, are one of the essential evidences to show biosimilarity, necessary for the conclusion on the subsequent clinical trials for the evaluation of the product developed through comparability.

6. When these studies are required, the following parameters should be observed for its proper conduction:
  - a. The pharmacokinetics study protocol should justify the inclusion of healthy volunteers or patients, considering the safety profile of the specific product.
  - b. Where available, intra-subject and inter-subject variability parameters should be observed for determination of the number of volunteers.
  - c. For selection of the dose used in the studies, the pharmacokinetics linearity data should be considered.
  - d. Sample collection schedule should assure the adequate characterization of the product plasma profile (concentration *versus* time), including a time equal to or higher than 3-5 times its elimination half-life.
  - e. The research project, the experimental protocol and the informed consent form should be submitted and approved by a Research Ethics Committee (REC).
  - f. Products plasma quantification should be performed by validated bioanalytical method, as determined by the Brazilian Collegial Board of Governors' Resolution (RDC) Resolution No. 27, of May 17, 2012.
  - g. A table containing individual values, (arithmetic and geometric) means, standard deviation and coefficient of variance of all the pharmacokinetics parameters related to the administration of the test and reference drugs should be presented.
  - h. It is recommended that the  $ASC_{0-t}$  and  $C_{max}$  parameters are transformed in natural logarithm. Rationales should be presented in cases where it is chosen to perform the statistical analysis in original scale data.
  - i. Analysis of variance (ANOVA) of the  $ASC_{0-t}$  and  $C_{max}$  transformed pharmacokinetics parameters should be performed to evaluate the effects of sequence and volunteer within the sequence, period, and treatment. In addition, ANOVA table containing source, freedom degree, sum of squares, mean square, **F** statistics, **p**-value, and intra- and inter-subject coefficients of variance should be presented.

- j. A 90% confidence interval (CI) should be built for the difference of mean transformed data of the test and reference drugs, for the  $ASC_{0-t}$  and  $C_{max}$  parameters. The obtained CI antilogarithm constitutes the 90% CI for the parameters geometric means ratio:  $ASC_{0-t \text{ test}}/ASC_{0-t \text{ comparator}}$  and  $C_{max \text{ test}}/C_{max \text{ comparator}}$ . The construction of this CI should be based on the residual mean square of the ANOVA obtained.
  - k.  $T_{max}$  will be analyzed as individual difference (= test-comparator), building 90% CI, using non-parametric test.
  - l. For studies with intravenous administration,  $ASC_{0-\infty}$  will be considered to be the primary endpoint. As for the subcutaneous studies,  $C_{max}$  and  $ASC$  will be considered supporting endpoints.
  - m. For multiple dose studies, the measurement of total exposure should be the area under the concentration-time profile from the zero time to  $\tau$  time through the dosage interval at steady state ( $ASC_{0-\tau}$ ), where  $\tau$  is the interval duration between the dosages and this is considered the primary endpoint. The minimum concentration at steady state ( $C_{trough \text{ ss}}$ ) should be measured at the end of a dosage interval before starting the next dose and the  $C_{max}$  will be the maximum concentration measured after the dose, and these are considered as secondary parameters.
  - n. Pharmacokinetics profiles of two products will be considered similar, if the extreme values of the 90% confidence interval of the geometric means ratio ( $ASC_{0-t \text{ test}}/ASC_{0-t \text{ comparator}}$  and  $C_{max \text{ test}}/C_{max \text{ comparator}}$ ) are higher than 0.8 and lower than 1.25.
  - o. Validated statistical programs should be used.
  - p. When necessary, proper statistical models, depending on the type of study (e.g., multiple doses), should be used.
7. For the secondary application, 10900 – CLINICAL TRIALS – Comparative pharmacokinetic studies for experimental drugs – Biosimilar – submitted as DDCM, final, clinical, analytical, and statistical report should be prepared, describing the study data, as per RE Resolution No. 895, of May 29, 2003. The report should be sent in PDF digital format, burned to a CD.
8. We recommend that the pharmacokinetics clinical trials are performed at ANVISA certified sites.

9. RDC Resolution No. 55/2010, RE Resolution No. 895/2003 and RDC 09/2015 were taken into consideration.
  
10. In cases where there is CETER evaluation during the drug clinical development, as per this Technical Note, the resubmission of subject 10846 – BIOLOGICAL PRODUCT – Addition: pharmacokinetics studies as per the Explanation Note No. 002/2015/GPBIO/GGPBS/SUMED/ANVISA will not be necessary. At the time of registration submission, the applicant should only present the Technical Opinion Letter of the pharmacokinetics clinical trials evaluation issued by CETER to the Management of Biological Products.

Brasília, 19/Apr/2016.

[on behalf of Eduardo Agostinho F. Fernandes]  
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