



ANVISA

Agência Nacional de Vigilância Sanitária

TECHNICAL NOTE 09/2015

Clarifications on relative bioavailability studies to show pharmacokinetic interaction for purposes of registration of Fixed-Dose Combinations or consent to Drug Clinical Development Dossier – DDCM

Coordination of Therapeutic Equivalence – CETER

Coordination of Clinical Research in Drugs and Biological Products – COPEC

General Management of Drugs – GGMED

Superintendence of Drugs and Biological Products – SUMED

Brazilian Health Surveillance Agency – ANVISA

BRACRO

Brasília, 03 September 2015.

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TECHNICAL NOTE No. 09/2015/CETER/GGMED/SUMED/ANVISA-Ministry of Health (MS)

It updates Technical Note no. 06/2014, which refers to the clarifications on relative bioavailability studies to show pharmacokinetic interaction for purposes of Fixed-Dose Combinations.

1. The update of Technical Note no. 06/2014/CETER/GGMED/ANVISA is necessary given two aspects:
 - a. The creation of a specific subject code for submission of relative bioavailability studies to show pharmacokinetic interaction.
 - b. The inclusion of the need for submitting pharmacokinetic interaction data also when arising from the scientific literature.
2. As determined in the Guide for Registration of New Fixed-Dose Combinations (ADF), published by Anvisa in 2010, and by the above-mentioned Technical Note, situations where possible pharmacokinetic interactions among the active ingredients may be considered by the conduction of relative bioavailability studies are the following:
 - a. registered mono-drugs have a well-established efficacy and safety profile, but the combination has not been studied yet in the doses and for the therapeutic indications that are intended to apply, or their efficacy and safety profile is not established by scientific evidence available in the literature.
 - b. the proposed ADF has one or more new active ingredients in the country.
3. For such cases, relative bioavailability studies are mandatory and should precede efficacy and safety clinical trials that will be conducted with the ADF.
4. Relative bioavailability studies performed to determine the pharmacokinetic interaction between drugs should be conducted using the reference drugs administered concomitantly *versus* reference drugs administered alone. To perform independent trials in order to assess pharmacokinetic interaction for each combined drug (e.g., in case of an ADF containing two drugs, two trials would be required: $R_1R_2 \times R_1$ and $R_1R_2 \times R_2$) is suggested.
5. In cases in which the ADF has the same active ingredients, in the same strengths and dosing regimen as a treatment schedule with concomitant use of mono-drugs that have their safety and efficacy profile established by scientific evidence available in the literature, pharmacokinetic interaction data should also be submitted for evaluation.

6. In order to be accepted by Anvisa, pharmacokinetic interaction data available in the literature should be original from articles published in indexed journals.
7. Such studies, both conducted by the company as original from literature, should be submitted for analysis by the Therapeutic Equivalence Coordination (CETER/GGMED/ SUMED/ANVISA) through a **primary petition**, by the subject code **10839 – Pharmacokinetic Interaction Studies for Consent in Clinical Trials**.
8. After completion of the petition analysis, CETER will submit an opinion to the applicant. This report should be included in the documentation to be submitted to Registration of New Combination (Situation 01 in the Guide) or to the request of Consent to DDCM (Situations 02 and 03 in the Guide).
9. We suggest that the submission of DDCM to COPEC, containing specific dossiers of clinical trials of safety or efficacy occurs only after issuance of the Conclusive Opinion by CETER about relative bioavailability studies to show pharmacokinetic interaction.
10. This technical note is current as of its publication.

Brasília, 03 September 2015.

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