A rocky path to the development of generic drugs

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The high complexity of n-3 fatty acids absorption process, along with the huge amount of endogenous fraction, makes bioavailability studies with these agents very challenging and deserving special consideration. Two previous trials were addressed to demonstrate bioequivalence (BE) between a new formulation of eicosapentenoic acid (EPA) + docosahexaenoic acid (DHA) ethyl esters developed by IBSA Institut Biochimique and a reference medicinal product present on the Italian market, both missing the target. In a first attempt, a standard single-dose crossover design was deemed unsuitable because of high variability of n-3 fatty acids and the influence of huge endogenous fraction. Whole blood levels of DHA and EPA were therefore compared after long-term (4 weeks) treatments in a randomized, parallel-group design. Twenty-four volunteers per group received 3 grams daily of Test of Reference drug; baseline levels of circulating DHA and EPA were assessed weekly, and a time-course from 0 to 8 hours was carried out after the last dosing. Data adjustments were conducted to subtract baseline levels to each subject, as well as to correct for the different DHA/EPA titration between study drugs. BE demonstration was not fully achieved, with the huge inter-subject variability being considered a major confound in the study. Data correction for the different DHA/EPA titration was also criticized [1]. The following trial had a classical randomized crossover design, with 8-week washout between treatments. A dose higher than those indicated in the clinical practice, 12-gram was administered as a single dose. Well aware of the relevance of high drug variability in this setting, the investigators adopted quite an original approach; out of an initial population of 50 volunteers, 10 subjects were selected for having very low circulating DHA and EPA levels at baseline. While this approach significantly reduced the overall variability, and enabled to demonstrate BE between study drugs, the sample size of the trial fell below the minimal acceptable number of subjects suggested by the European Medicines Agency (EMA) guideline, which is 12, thereby failing to accomplish all of the regulatory criteria for BE demonstration [2]. Eventually, BE was demonstrated according to the criteria established by the EMA Guideline on the Investigation of Bioequivalence by considering the free fractions of plasma EPA and DHA as the primary end-point of measure. We found that the free fractions represent a better and more sensitive end-point for bioequivalence investigations on n-3 fatty acids, since: *i*) the overall and intra-subject variability of PK parameters was markedly lower compared to the same variability calculated on the total DHA and EPA fractions; *ii*) the absorption process was completed within 4 hours, and the whole PK profile could be drawn within 12-15 hours from drug administration [3].

1. Rusca A et al. Eur J Clin Pharmacol 65: 503-510, 2009.
2. Galli C et al. Br J Clin Pharmacol 74: 60-65, 2012.
3. Scarsi C et al. Prostaglandins Leukot Essent Fatty Acids 96: 11-16, 2015.