



Deteriorating Quality in Global Trials



Until the late 80's, Phase III trials were conducted essentially in North America and Europe.

Jean-Pierre Tassignon, MD, PhD,
President and CEO
Crossover CRI AG
jean-pierre.tassignon@crossover-cri.com
www.crossover-cri.com

A recent study (*2010 Pharmaceutical R&D Factbook*) indicates that the decade-long drop in the overall success rate of pharmaceutical R&D continued in 2009. The authors found that "the number of experimental drug projects terminated at the final Phase III stage of development had doubled in 2007-2009 compared with 2004-2006."

We can postulate that suitable dose-effect relationships were demonstrated in Phase II clinical trials for these failed drug projects. Rather than infer that preclinical research through Phase II has suddenly become error-prone, there is merit in assessing the validity of Phase III clinical trials today.

Until the late 80s, Phase III trials were conducted essentially in North America and/or Europe. The drug pipeline delivered twice as many innovative medicinal products annually. Clinical research globalized over the last two decades by following the path of diminishing GDP per capita. The evidence comes from plotting the year of the first FDA inspection in any particular country versus GDP per capita in that country.

Our research evaluated the clinical trial participation of sites in North America and in Europe in Phase II and III industry trials in the period 2004-2006 compared with 2007-2009. North America participated in 60% of Phase II trials worldwide in both periods, twice more than Europe. The complexity of trial protocols is growing fast in Phase II, driving up the costs of procedures and labs. According to a Tufts Center for the Study of Drug Development news item from May 5, 2010 the high medical technology content of Phase II studies may explain the dominance of North American sites in Phase II trials.

The same report notes that Phase III protocols are less likely to increase in complexity. Hence, the position of North America in Phase III is seriously undermined by globalization: North American sites participate only in 30% of Phase III trials worldwide. In 2007-2009, North

American and European sites have seen their respective shares in Phase III trials decline in favor of the rest of the world.

We can assume that the diminishing participation of North American and European sites in Phase III trials is even worse in terms of patients enrolled. Understandably, it is cost effective for sponsors to include sites from low-cost countries in large Phase III studies, where, in addition, participants are potentially more incentivized. Indeed, the lower the local standard of care compared to that offered in the trial, the greater the incentive for patients to take part. To make matters worse for sites in North America and Europe, recruitment periods are being closed prematurely as a function of global sample size completion.

The quality of Phase III trials is weakened further by massive differences between sites. Biostatisticians do not censor data for these conditions. Just one example regarding concomitant medications: WHO puts a ceiling of 1% of market value on the amount of medicinal products in North America and most of Europe which are counterfeit, but the estimate is at least 10% with no ceiling for other regions of the world. The most puzzling paradox is that health authorities in North America and Europe accept evidence from countries from which they do not recognize the diplomas of doctors and other health-care personnel who produce the data.

In conclusion, as addressed in this space in April 2010, data from healthcare systems with health outcomes significantly worse than in North America and Europe comes cheaper, but may jeopardize the overall success rate of new drug projects coming out of Phase II. □