The Global Substance Test Dilemma at the Beginning of the 21st Century

There has quite clearly been an embarrassing gap in the provision of adequate measures to predict the interactions of consumer-relevant natural or synthetic substances with the human body, prior to human exposure, while also taking into account typical environments and individual genotypic specificities. The human population has more than doubled over the last 50 years, whilst the registration of chemicals at the Chemical Abstract Service has increased by two orders of magnitude, from about 212,000 in 1965 to about 88.7 million in 2006 (1), as illustrated in Figure 1.

The variety and potential dosage of chemicals to which each human individual is exposed, have both increased exponentially. The US Environmental Protection Agency (EPA) estimated, based on registrations, a total of 8 million different chemical entities, with a total manufacturing yield of about 12.2 trillion kilogrammes in 2006 (2). Pharmaceuticals, with several thousand approved drugs, represent a small, but, due to direct internal human exposure, very sensitive fraction of these chemicals. In contrast to all other chemicals, they are specifically designed to effectively combat a disease with an acceptable risk-to-benefit balance in patients. According to the United Nations (UN) reporting system (3, 4), more than 624 pharmaceutical products have been banned, withdrawn, severely restricted, or not approved by governments since the thalidomide disaster in the late-1950s. The regulatory bodies have significantly increased their legal frameworks in response to the most devastating misjudgements of the last 50 years (which are summarised in Table 1), and for animal welfare reasons.

The first powerful motivation for revisiting conventional substance testing approaches, i.e. in vivo testing, was the scientific concept of the Three Rs (Replacement, Reduction and Refinement), outlined by Russell and Burch (5), which was implemented in the European Council Directive 86/609/EEC of 24 November 1986 (6) on the use of experimental animals, and more firmly in the new...