interesting that the Sponsor was able to obtain on the package labeling this specific reference to lack of carcinogenicity in laboratory animals deficient in TNFα. The Remicade labeling pertaining to carcinogenicity was again revised in the 2003 PDR (28). This labeling would indicate that the 6-month chronic study of cV1q in mice discussed previously was actually a tumorigenicity study; although tumorigenicity is not mentioned in the EMEA Scientific Discussion document comments on this 6-month study. As the dose levels and duration are the same, this is likely one and the same study. The Remicade labeling in the 2003 PDR has dropped the reference to the lack of tumorigenicity in TNFα-deficient mice provided in the 2002 PDR, and stated that a 6-month repeated-dose study with cV1q anti-mouse TNFα found no indication of tumorigenicity in mice.

In summary, the lack of cross-reactivity and a relevant animal species, the expanded clinical population, and the extended clinical dosing regimen provide for a fascinating Case Study of Remicade. Remicade was first approved for use in patients with Crohn's disease in which a total of three doses of the biologic were to be administered. As infliximab was found to be cross-reactive only with TNFα in chimpanzee, an endangered species, the regulatory authorities did not have serious issues with the lack of repeated-dose administration non-clinical toxicity data to support the short duration of clinical exposures. Nevertheless, the Sponsor was concerned with the Pregnancy category labeling and developed a murine surrogate for use in reproductive toxicity testing in mice. The negative data generated in these studies allowed the Sponsor to use a Pregnancy Category B in the labeling package insert. It is interesting to note that in moving Remicade forward in the treatment of rheumatoid arthritis, the availability of safety data for the biologic in thousands of Crohn's disease patients did not preclude the Sponsor from conducting a chronic toxicity/tumorigenicity study of the murine analog. The submission of novel carcinogenicity studies not involving administration of the biologic in question to support a labeling statement is also a remarkable component of this Case Study, as is the progression in the PDR (consecutive years) of the studies included in the carcinogenicity section of the package labeling.

6. CONCLUSIONS

Drug development is a dynamic, ever-changing process that is not easily compartmentalized into a checklist of non-clinical toxicity studies that should be conducted as one moves towards marketing approval. Despite the challenges in study design, the questions to be addressed in these studies generally remain the same. Characterization of target organs, dose–response relationships and correlative systemic exposures, and reversibility of any observed effects are all major issues that must be addressed in laboratory animals prior to administration of the drug in the first Phase I clinical trials.