Developmental and Reproductive Toxicity Testing

1 INTRODUCTION

The goal of testing the developmental and reproductive toxicity of drug candidates in laboratory animals is to predict which agents would adversely affect the ability to achieve and maintain pregnancy and for normal development of offspring in humans and to allow evaluation of the potential risks to patients. This testing involves an extensive battery of studies based historically on guidelines promulgated by the U.S. Food and Drug Administration (FDA) in 1966 (see FDA, 1966, 1982, 1984; D'Aguanno, 1973) and subsequently modified by the International Conference on Harmonisation (ICH). These guidelines established three basic types of studies, segments I, II, and III, that are based on dosing during sequential phases of the reproductive cycle. These guidelines represented a dramatic increase in the extent and sophistication of testing expected of new drug candidates. The impetus for this intensified interest was the tragic epidemic of phocomelia and other congenital malformations caused in the early 1960s by the exposure of pregnant women to the sedative thalidomide. (For an excellent discussion of the history of the thalidomide tragedy, see pp. 228–249 in Schardein (1993)]. Table 1 presents the most recent guidelines.

The types of developmental and reproductive toxicity studies performed prior to 1993 and the methods used have been extensively documented (see Palmer, 1981; Christian, 1983; Heinrichs, 1985; Heywood and James, 1985;

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