Table 3 Effect of Celecoxib Treatment on Tumor Multiplicity in the APC Min Mouse Model

		Tumors/mouse	
Drug	Dose in diet (ppm)	Early treatment (30–80 days)	Late treatment (55–80 days)
Vehicle	0	22.4 ± 9.0	22.9 ± 6.8
Celecoxib	150	15.8 ± 9.5	18.0 ± 7.6
	500	15.8 ± 4.6	16.3 ± 6.2
	1500	6.5 ± 4.2	11.1 ± 6.8
Piroxicam	50	5.2 ± 4.0	7.9 ± 4.8

Source: Refs. 34,47,48.

genetic model of human FAP, celecoxib, which selectively inhibits COX-2, showed effectiveness for prevention (i.e., "early" treatment before development of adenomatous polyps) and regression (i.e., treatment after most adenomatous polyps are established), comparable to that of the positive control of piroxicam. Celecoxib caused dramatic reductions in the multiplicity of tumors in a dose-dependent manner (Table 3) (34,47,48).

Additionally, in the rat colon cancer model induced by azoxymethane, treatment with celecoxib for 11 weeks resulted in a 40% reduction in aberrant crypt foci that was similar to that observed for the positive control, sulindac, given at its MTD (320 ppm) (34,49). When administered for one year in the diet, 1500 ppm of celecoxib reduced tumor incidence by 93%, surpassing the results observed in similar studies with various non-steroidal anti-inflammatory drugs (NSAIDs) (34,50).

In the review document, the medical reviewer clearly indicated that the approval of celecoxib for the reduction of the number of adenomatous colorectal polyps in FAP patients was supported by (1) evidence from animal colon tumor models, demonstrating a reduction in the incidence and multiplicity of tumors with its exposure, and (2) numerous clinical studies, mostly small, uncontrolled series, demonstrating the ability of other NSAIDs, notably sulindac, to reduce colorectal polyps in FAP patients (34). This example adequately illustrates how preclinical animal models, when coupled with the well-understood pathophysiology of a disease, can be successfully used to support the efficacy claim for regulatory approval.

3. UTILIZING THE PRECLINICAL DATABASE TO ADDRESS SAFETY CONCERNS

When the FDA reviews a submitted NDA package, any safety concerns raised during the preclinical or non-clinical phase are given special attention