the scientists at Hoechst Marion Roussel (now Sanofi) were not aware of it at the time, it was later determined that Seldane® (Terfenadine) is actually a prodrug and the corresponding carboxylic acid metabolite Allegra® (Fexofenadine) is the true biologically active compound. At the same time, Seldane® (Terfenadine) is a potent hERG channel blocker ($IC_{50} = 10\,nM$[34]), but its rapid removal from the systemic circulation by CYP450 3A4 metabolism prevents it from achieving a significant plasma concentration. Therefore, under normal circumstances, Seldane® (Terfenadine) does not impact cardiac function, as it is rapidly eliminated. If, however, CYP450 3A4 activity is inhibited by other drugs, such as ketoconazole and erythromycin, plasma concentrations of Seldane® (Terfenadine) can increase rapidly, leading to adverse cardiovascular effects (e.g., ventricular arrhythmia, ventricular tachycardia, torsades de pointes, and sudden cardiac death).[35] In other words, it is the combination of suppression of CYP450 3A4 metabolism (which alters pharmacokinetic parameters of the drug) and potent hERG blockade of the parent compound that produce the potentially deadly effects observed with Seldane® (Terfenadine).

As the commercialization of Seldane® (Terfenadine) was coming to an end, the small biotech start-up company Sepracor (now Sunovion) was actively attempting to take advantage of the discovery of the active metabolite of Seldane® (Terfenadine). The scientist at Sepracor correctly hypothesized that this active metabolite, which was eventually marketed as Allegra® (Fexofenadine), would possess all of the positive attributes of the parent compound (e.g., non-sedating antihistamine, good PK properties), but not the cardiovascular risk profile. They based this hypothesis on the observation that Allegra® (Fexofenadine) had no activity as a hERG channel blocker (keep in mind that relationship between the hERG channel and cardiovascular risk had not been firmly established at the time). This hypothesis, of course, turned out to be correct. Sepracor secured a patent on the metabolite and then licensed the compound to Hoechst Marion Roussel (now Sanofi) in 1993. By 2004, annual sales of Allegra® (Fexofenadine) reached $1.87 billion,[36] and the drug was approved for over the counter sales in 2011, further broadening the market.[37]

The discovery and development of Seldane® (Terfenadine) and Allegra® (Fexofenadine) teach some important lessons. First, the safety of a therapeutic agent is controlled by more than the physical properties of the therapeutic agent itself. Metabolites can create significant safety risks which must be evaluated as candidate compounds are considered for further progression in the drug discovery and development process. Second, and perhaps more importantly, the pharmacokinetic profile of one drug can be significantly impacted by the presence of a second drug. Although this concept is well known to modern drug discovery scientists (and is the basis for screening candidate compound for CYP450 inhibition), it was novel science when this story was unfolding. Finally, understanding the role of metabolites in biological activity can be the key to identifying new therapeutic agents. In this case, Hoechst Marion Roussel's missed out on a major opportunity by