Merck & Co formally announced FDA approval for Dulera today, marking the third combination inhaled asthma therapy drug to reach the US market, a notable event given the FDA’s intense scrutiny of the safety of these products over the last couple of years.

However, at the same time the FDA was waving through Dulera another company attempting to bring a similar product to market appears to have been stopped at a red light. An announcement from SkyePharma today indicates that the chances of the British company winning approval for its candidate, Flutiform, at least on commercially viable terms, has dropped from slim to none. Why Dulera has succeeded where Flutiform appears to have failed has left many observers scratching their heads.

Already approved

Both Dulera and Flutiform are combinations of drugs already on the market. The former is the inhaled corticosteroid (ICS), mometasone furoate, combined with the long acting beta agonist (LABA), formoterol fumarate; the latter the ICS fluticasone propionate and the same LABA, formoterol.

Formoterol is sold as Foradil by Novartis, a product which lost patent protection four years ago. Mometasone was launched by Schering-Plough as an ICS called Asmanex in 2004, while fluticasone is the ICS used by GlaxoSmithKline in Advair, which it also sells individually at Flovent; its specific patent expired in 2004.

Dulera was actually approved two days ago, according the FDA’s website; the delay in the news breaking remains another unanswered question today.

This aside, the product is not predicted to be hugely important commercially speaking for the US drug maker. The product, inherited with the takeover of Schering-Plough, is forecast to generate $409m by 2016, according to consensus data from EvaluatePharma. However, given the recent scrutiny of LABAs by the FDA and question marks over whether approval would be granted at all, these forecasts could now rise.

Harbouring fears

The FDA has long been harbouring fears that long term use of combination therapies in asthma might actually increase the occurrence of severe asthma attacks, ultimately causing more deaths. Extensive study and debate ended with the addition of black box warnings on the two products already on the market - GlaxoSmithKline’s Advair and AstraZeneca’s Symbicort - warnings that will also be carried by Dulera, its label shows.

In fact, it is very likely that approval of Dulera was being held up whilst the FDA concluded its debates on this subject, as the product was filed 11 months ago (New LABA warnings unlikely to make big players pause for breath, June 3, 2010).

As part of the review of the LABAs, the FDA decided that further long term safety studies were going to be required of any product that contains these drugs, however the final size or scope of these studies has not been determined. A Merck spokeswoman told EP Vantage today that Merck is aware of the requirement to conduct these studies.

As to what has happened with SkyePharma is not immediately clear. The value of the British company has declined considerably over the last couple of years along with confidence in the product making it to market. After today’s share price fall, down 15% to 29p, the company is worth just £7m. Only a few years ago it was the pride of UK biotech with a market cap close to £400m ($599m).

Surprising news

SkyePharma had already received a complete response letter raising a number of “substantive issues”, which would probably have spelt further clinical work. In a downbeat statement today following further talks with the
regulator, the company announced that meeting the FDA’s requirement would involve significant additional work, including a large post-approval safety study.

Whether this refers to the FDA’s requirement for all LABA containing drugs to undergo long term safety trials, or is something particular to Flutiform, is not immediately clear. Considering the drug's components are already on the market, like Dulera's, it is hard to believe it is potentially much more dangerous. Some analysts have speculated that possibly the excipient used by Skye in Flutiform, the inactive part of a drug used to carry the active component, has caused the problems, although this could not be confirmed immediately.

It could simply come down to the fact that Merck has decided to take the hit of the cost of these long term safety studies, whilst SkyePharma has had to conclude it simply cannot afford it.

Either way, having conducted five phase III trials, all of which have been positive, a certain amount of sympathy can be felt for SkyePharma today, which has struggled for years and jumped through numerous FDA hoops to get this far.

Unfortunately, it now looks certain that US partner Abbott Laboratories will wash its hands of this project (Flutiform delay no surprise, but a grim outcome, January 22, 2010). Which means it could be game over for Flutiform, in the US at least, and leaves SkyePharma having to make tough decisions.