Lotronex challenge raises timing issues

Due to the various hard and fast deadlines included in the US Hatch-Waxman framework, the early stages of paragraph IV cases usually follow a rather predictable timeline. Once an abbreviated new drug application (ANDA) containing a paragraph IV certification is accepted for filing by the Food and Drug Administration (FDA), the ANDA applicant has to notify the new drug application (NDA) holder and the patent owner within 20 days. That notification must include a detailed statement of the factual and legal basis why the patent or patents at issue are invalid, unenforceable or will not be infringed. Upon receipt of the notification, the NDA holder and patent owners have 45 days in which to initiate a patent-infringement suit that triggers a 30-month stay of final ANDA approval, starting from the latest date on which a notification was received.

Because the FDA updates its online listing of paragraph IV certifications every two weeks, the first challenge to a product is usually posted on the agency's site a few weeks ahead of any litigation. "When events in a Hatch-Waxman case do not follow the usual timeline, something interesting may be going on," observes Thomson Reuters, which maintains a database of paragraph IV challenges.

In the case of Prometheus Laboratories' irritable bowel syndrome (IBS) treatment Lotronex (alosetron hydrochloride), the events have not followed the normal course. Although Prometheus initiated an infringement suit against Boehringer Ingelheim's Roxane Laboratories on 14 January 2011, the FDA's website still had not listed any paragraph IV challenge to Lotronex tablets as of the 21 February update.

Lotronex is covered by two patents listed in the FDA's Orange Book. US patent 5,360,800 includes both drug-substance and drug-product claims, and expires on 13 January 2013. However, the case focuses on US patent 6,284,770, which includes claims directed to treating women with severe diarrhoea-predominant IBS, and expires on 5 October 2018. The '770 patent was recently re-examined.

If an ANDA includes a paragraph IV certification at the time of submission, the applicant cannot send its notification letter until the FDA formally accepts the ANDA for filing. This delay affects the notification date and, as a result, the date upon which any 30-month stay of approval expires. If, however, an ANDA that was originally submitted without a paragraph IV certification is subsequently amended to include one, the ANDA applicant must send its notification letter on the same day that it submits its amendment and not wait for formal FDA acceptance. "This may be a source for the delay in the FDA posting of the alosetron challenge," Thomson Reuters believes. However, there appears to be more to the story.

In its lawsuit, Prometheus alleges that Roxane's notification letter dated 6 December 2010 addressed the original claims of the '770 patent, rather than the re-examined claims. Therefore, Prometheus argues, Roxane did not provide Prometheus with the required full and detailed explanation of the basis of the paragraph IV certification. For the same reason, Roxane's certification to the FDA was defective.

According to Roxane's response, it appears that in January 2011, Roxane provided the FDA with an additional paragraph IV certification to the '770 patent, and Prometheus with an additional notice letter. "Presumably the 30-month stay will run from the date of receipt of whichever notification letter is deemed to have been sufficient by the FDA," Thomson Reuters concludes.

KEY DETAILS: LOTRONEX

Brand:	Lotronex
Active ingredient:	alosetron hydrochloride
Delivery form:	0.5mg and 1mg EQ tablets
Brand owner:	Prometheus
Annual US brand sales:	US$30.4 million in 2009
First paragraph IV filing accepted by FDA:	6 December 2010
Known paragraph IV filers:	Roxane
Patents at issue – expiry dates:	6,284,770 – 5 October 2018
District court location:	New Jersey
Litigation references:	Prometheus vs Roxane 2:11-cv-00230
Other FDA Orange Book patents with expiry dates:	5,360,800 – 13 January 2013

Figure 1: Key details of paragraph IV challenges to Prometheus' Lotronex (alosetron) irritable bowel syndrome treatment in the US (Source – Thomson Reuters)

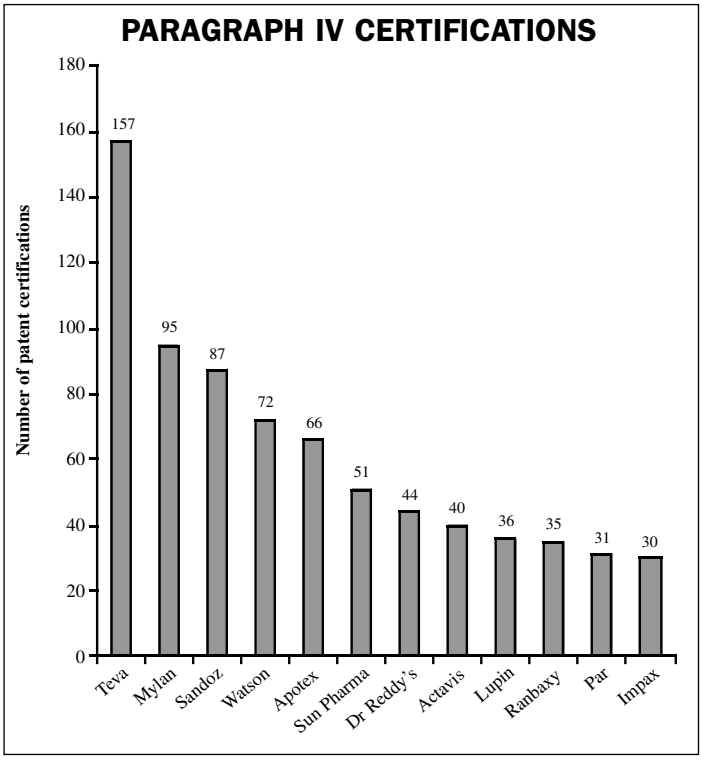

Figure 2: Numbers of paragraph IV patent certifications recorded by Thomson Reuters to 31 December 2010 (Source – Thomson Reuters)