

# Litigation Notes

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## CEPHALON'S AMRIX LITIGATION

We read the post-trial briefs of both sides in the patent infringement case brought by **Cephalon** and **Eurand** against **Mylan** and **Teva's** Barr Laboratories in connection with Amrix, Eurand's extended release skeletal muscle relaxant licensed to Cephalon. The trial took place last October before Judge Sue Robinson of the U.S. District Court in Delaware, and since then, the parties have filed a total of six briefs. Three of the briefs are devoted to infringement issues, and the other three are devoted to validity and enforceability. Ironically, Mylan has conceded infringement of all asserted claims of the two patents at issue and Barr has conceded infringement of all but two of them, and therefore it seems to us that the generics must win on validity or enforceability if they are going to prevail. Accordingly, this report is focused on the validity and enforceability issues.

**In our analysis, the case was litigated with unusual aggressiveness by both sides, making it less obvious which side is going to win, but we think that on the merits, Teva and Mylan have the stronger position. We think that Judge Robinson is probably less inclined to tilt the outcome in favor of the patentees than some of the other judges in Delaware, but nevertheless, the Delaware federal court definitely favors big company patentees. Accordingly, although we think the better bet is on Teva and Mylan, we do not have a strong conviction that Judge Robinson will decide in their favor.**

In general, the patents in this case cover an extended release version of cyclobenzaprine, a skeletal muscle relaxant that has long been widely available in an immediate release format. Since infringement is largely out of the case at this point, the primary issue is whether the two asserted patents are invalid for obviousness. The generics' position is that the claimed elements of the Amrix patents, including the multiparticulate platform, the dissolution profile, the pharmacokinetic parameters and the dosing requirements were all disclosed in the prior art and that one of ordinary skill would have had a reasonable expectation of success in combining them. Cephalon's position is that there are some elements of the claims that, in fact, were not disclosed in the prior art, and further, that the generics failed to prove that a skilled artisan would have combined the elements so as to create the claimed dissolution profile.

Cephalon's lawyers (primarily Fish & Richardson) made a seemingly persuasive argument that the inventors of extended release cyclobenzaprine disregarded conventional wisdom in designing Amrix. The conventional wisdom for extended release drugs is that they should reduce the peaks and valleys of plasma concentration associated with immediate release administration so as to deliver a more consistent dosage level of the drug throughout the day, thus assuring efficacy while decreasing the likelihood of side effects. The Amrix inventors, however, opted for a higher  $C_{max}$  and a lower  $C_{min}$  than would occur if an

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immediate release version of cyclobenzaprine were administered three times daily. The fact that this formulation was successful without decreased efficacy or increased sedation is said to be an “unexpected result” that trumps any possible showing of prima facie obviousness.

In their reply brief on validity, Mylan and Barr (represented by Wiley Rein and Winston & Strawn, respectively) address the higher  $C_{max}$ , lower  $C_{min}$  argument described above, stating that there is nothing in the patent claims that limits the claimed invention to a higher  $C_{max}$ . Importantly, they explain that the actual  $C_{max}$  and  $AUC_{1-168}$  of Flexeril (the immediate release version of the drug) falls squarely within the claimed ranges. In our view, this argument should be sufficient to rebut Fish & Richardson’s theory on unexpected results.

Cephalon also argues that there are at least some limitations of the patents that are not disclosed in the prior art at all, the first of which is that the prior art does not disclose a dosage form of cyclobenzaprine that provides a therapeutically effective plasma concentration over a 24-hour period. Second, it says that no pharmacokinetic parameters for extended release cyclobenzaprine had ever been disclosed in the prior art. The generics counter that by using the plasma concentration of Flexeril over a 24-hour period, it is obvious what the required plasma concentrations need to be. The plaintiffs’ contention that the prior art does not disclose these limitations, they say, is simply wrong, since Flexeril itself has them.

Next, Cephalon argues that the generics failed to prove that a person of skill in the art would have targeted the pharmacokinetic profile described in the claims. It says that no pharmacokinetic parameters had ever been established for extended release cyclobenzaprine, and that there was no teaching in the prior art that any particular profile would provide a therapeutically effective plasma concentration of cyclobenzaprine over a period of 24 hours. Once again, the generics argue that a person of ordinary skill would have targeted bioequivalence to Flexeril in seeking to develop an extended release version of cyclobenzaprine.

Although the argument that the person of ordinary skill would use the parameters of Flexeril as a target for the pharmacokinetics of extended release cyclobenzaprine seems very solid, Cephalon came up with a post-trial argument that FDA guidance would only motivate the person of ordinary skill to target Flexeril in steady state administration, not in a single administration. The generics respond by pointing out that there was no evidence at trial that there is a meaningful distinction between steady state administration and single administration, since this argument was only introduced in the post-trial phase of the case.

Cephalon makes an extensive argument that the person of ordinary skill would have had a low expectation of success that extended release cyclobenzaprine with the Flexeril parameters would be therapeutically effective. In support, it supplies a long list of uncertainties that would have confronted the ordinary drug developer, such as uncertainty about permeability of cyclobenzaprine in the large intestine, whether the “linear” pharmacokinetics of immediate release cyclobenzaprine were applicable to the large intestine, and whether cyclobenzaprine would be degraded by microorganisms in the colon. Unlike oxybutynin, it said, where there was a reasonable expectation that the drug would be absorbed in the colon, here there is no basis for a person of ordinary skill to infer that colonic absorption would occur. Colonic absorption is important for extended release drugs although not necessarily so for their immediate release counterparts.

The generics countered the reasonable expectation argument by stating, first, that a product that is bioequivalent to Flexeril would reasonably be expected to be therapeutically effective. Second, they noted that the lipophilicity of cyclobenzaprine, as their expert testified, was a good indicator of whether it would be well-absorbed in the colon. True, they said, colonic absorption can be more accurately predicted by looking at other factors as well, but lipophilicity is a good indicator of permeability.

The generics also argue that if the use of a higher  $C_{\max}$  and a lower  $C_{\min}$  is the essence of the invention, then, because the higher  $C_{\max}$  and lower  $C_{\min}$  are not described in the specification, the claims of the patents are not enabled, are not sufficiently described and are fatally indefinite. It is true that these features are required of a valid patent and the lack thereof could be troublesome for Cephalon here.

A more persuasive flaw in the patents, in our view, is the inventors' failure to describe a best mode. The law requires disclosure of the best mode known to the inventor at the time the patent application was filed. The generics argue that one of the inventors, Dr. Venkatesh, had preferred dew points to use in the coating steps in making the formulation. Cephalon took the position that Dr. Venkatesh did not have an optimal dew point for the incoming air, and that for this reason it was not described in the patents, but this denial is in conflict with numerous internal documents and with Dr. Venkatesh's statements to the FDA. Further, Dr. Venkatesh subsequently filed a patent application on the dew point, seemingly conflicting with the argument that the dew point is a routine production detail.

The generics argue that the failure to disclose the optimal dew point not only invalidates the patents, but also constitutes inequitable conduct insofar as he represented to the PTO that he did not have a best mode. The inequitable conduct argument could conceivably be successful, but the courts are not receptive to inequitable conduct arguments, and in our view, the better bet is that it will be rejected in this case. However, the failure to disclose the best mode seems more serious to us and could well be the ultimate reason for invalidation of the patents.