

# EXHIBIT D

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

BOEHRINGER INGELHEIM	)	
INTERNATIONAL GMBH and BOEHRINGER	)	C.A. No. 05-700 (***)
INGELHEIM PHARMACEUTICALS, INC.,	)	
Plaintiffs,	)	
v.	)	
	)	
BARR LABORATORIES, INC.	)	
Defendant.	)	

**SUPPLEMENTAL EXPERT REPORT OF ERIC V. ANSLYN, Ph.D.**

**A. Dr. Bartlett's Report**

1. I have reviewed the expert report of Paul A. Bartlett and been asked to respond to some of the opinions therein.

2. While I disagree that, in order to be a person of ordinary skill in the art, an individual must have the level of education and/or experience that Dr. Bartlett describes, the opinions expressed in my reports would not change if I applied his definition instead of the definition contained in my initial report.

3. Nothing in Dr. Bartlett's report changes my opinions set forth in my March 28, 2007 report.

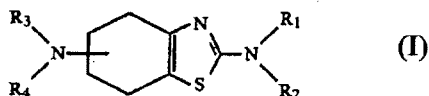
**1. The German Applications Do Not Disclose Halogen-Substituted Phenyl Moities at the R<sub>1</sub> Position.**

4. Dr. Bartlett incorrectly suggests several times that my March 28 report focused on the fact that claim 1 in the first German application does not include halogen-substituted phenyl rings at the R<sub>1</sub> position while claim 1 of the '812 patent does. While it is correct that the skilled artisan would understand that claim 1 of the first German application does not include such substituents, but claim 1 of the '812 patent does, my analysis was broader. I pointed out that the skilled artisan would understand that General Formula I of both German Applications

does not include halogen-substituted phenyl rings at the R<sub>1</sub> position while General Formula I of the '812 patent does. *See, e.g.*, Anslyn March 28 Rep. ¶ 45.

5. General Formula I is set forth at the very beginning of the German Applications, and both defines the scope of the invention of the German Applications and establishes the context for reading the entire disclosure of those applications. A skilled artisan would possess this understanding because, among other things, the very first sentence of the disclosure of the first German application reads:

This invention relates to new tetrahydro-benzthiazoles of general formula



the enantiomers and acid addition salts thereof, particularly the physiologically acceptable acid addition salts thereof with inorganic or organic acids, and processes for preparing them.

Exh. 53 at BARR28270. The second German application refers back to the first German application, stating “German Patent Application No. 34 47 075.1 describes tetrahydro-benzthiazoles of general formula [structure] (I)” and then completes the sentence in identical fashion. BARR209357. Explicit definitions of the R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> substituents of General Formula I follow in both applications. *See* Ex. 53 at BARR028270-71; BARR209358.

6. Dr. Bartlett agrees that claim 1 of the first German application does not disclose halogen-substituted phenyl rings at the R<sub>1</sub> position. *See* Bartlett ¶ 52. However, the definitions of R<sub>1</sub>-R<sub>4</sub> of claim 1 of the first German application are identical to the definitions of R<sub>1</sub>-R<sub>4</sub> of General Formula I of both German applications. Ex. 53 at BARR028270-71, BARR028314; BARR209357-58. Accordingly, under Dr. Bartlett’s analysis, General Formula I of the German applications does not disclose halogen-substituted phenyl rings at the R<sub>1</sub> position.

7. I disagree with Dr. Bartlett's opinion to the extent he asserts that the skilled artisan reading the methods of synthesis (d) and (e) of the German applications would understand them to disclose the synthesis of compounds with halogen-substituted phenyl moieties at the R<sub>1</sub> position. In addition, I disagree with Dr. Bartlett's opinion to the extent he asserts that the skilled artisan reading the synthetic methods (d) and (e) of the German applications would understand them to disclose compounds which have a halogen-substituted phenyl group at the R<sub>1</sub> position as starting materials, intermediates, or final products.

8. As I explained in my original report and above, the skilled artisan would understand that General Formula I of the German applications does not include halogen-substituted phenyl rings in the definition of the possible substituents at the R<sub>1</sub> position.

9. A skilled artisan would understand synthetic method (d) to describe the synthesis of compounds within General Formula I. Synthetic method (d) begins with the phrase "In order to prepare compounds of general formula I . . .", and a skilled artisan would read the description that follows in (d) in the context of that language. A skilled artisan therefore would not understand synthetic method (d) to disclose compounds or the synthesis of compounds with a halogen-substituted phenyl ring at the R<sub>1</sub> position, because those compounds are not encompassed by the group of compounds in General Formula I. The "wherein at least one of the groups R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or R<sub>4</sub> . . ." clause in the first sentence would be understood by a skilled artisan to indicate that the method is directed to making compounds defined by General Formula I, not a broad group of compounds unlimited by the bounds of General Formula I.

10. The same is true with respect to section (e). A skilled artisan would understand synthetic method (e) to describe the synthesis of compounds within General Formula I. Synthetic method (e) begins with the phrase "In order to prepare compounds of general formula I

. . .”, and a skilled artisan would read the description that follows in (e) in the context of that language. A skilled artisan therefore would not understand synthetic method (e) to disclose compounds or the synthesis of compounds with a halogen-substituted phenyl ring at the R<sub>1</sub> position, because those compounds are not encompassed by the group of compounds in General Formula I. The “wherein at least one of the groups R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or R<sub>4</sub> . . .” clause in the first sentence would be understood by a skilled artisan to indicate that the method is directed to making compounds defined by General Formula I, not a broad group of compounds unlimited by the bounds of General Formula I.

11. Dr. Bartlett relies on the German applications’ use of the term “hereinbefore” for his opinions regarding the disclosures of synthetic methods (d) and (e) in the German applications. *See* Bartlett ¶¶ 59-66. I do not believe the skilled artisan would interpret the word “hereinbefore” in those synthetic methods to change the fact that the methods are defined as making compounds of General Formula I.

12. Dr. Bartlett states that “inherently, the synthetic routes disclosed in the German priority applications would reasonably enable one of ordinary skill to make diaminotetrahydrobenzthiazoles with halogenated benzyl or other phenylalkyl groups as R<sub>1</sub> substituents.” Bartlett ¶ 57. Regardless of the accuracy of Dr. Bartlett’s assertion, as discussed above, the skilled artisan would not understand synthetic methods (d) or (e) to disclose either compounds, or the synthesis of compounds, with a halogenated phenyl group at the R<sub>1</sub> position. The skilled artisan would also not understand from either synthetic method (d) or (e)—or anything else in the German applications—that the inventors had made, or had contemplated making, compounds with a halogenated phenyl group at the R<sub>1</sub> position.

13. The skilled artisan would understand that the phrase “wherein the above mentioned phenyl nuclei may be substituted by 1 or 2 halogen atoms” of R<sub>1</sub> of claim 1 of the '812 patent is broader than the phrase “whilst the phenyl nucleus may be substituted by fluorine, chlorine or bromine atoms” of R<sub>3</sub> of General Formula I of the German applications. The skilled artisan would have that understanding because there are halogen atoms other than fluorine, chlorine and bromine: for example, iodine. Therefore, Dr. Bartlett's opinion does not explain how all of the compounds encompassed by claims 1 and 2 of the '812 patent as understood by the skilled artisan are disclosed in the German applications.

**B. The '086 and '812 Patents**

14. The skilled artisan would understand that each of claims 3-5 and 9-10 of the '812 patent encompasses multiple different compounds—from dozens to thousands of compounds. The skilled artisan would also understand that the phrase “2-Amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole” has the same meaning in claim 7 of the '812 patent and claims 9, 19, 29, and 39 of the '086 patent.

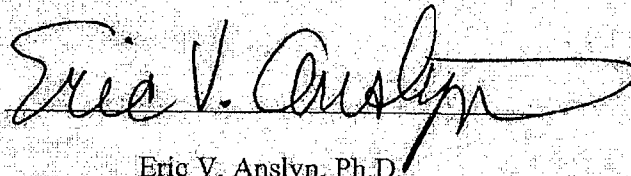
15. Because claim 8 of the '812 patent is dependent upon claim 3 of the '812 patent, the skilled artisan would understand that claim 8 encompasses at least thousands of pharmaceutical compositions.

16. The skilled artisan would understand that a natural result flowing from practicing the methods of at least claims 8, 9, 18, 19, 28, 29, 38, and 39 of the '086 patent would be the formation of the claimed compounds in both protonated (acidic) and unprotonated (free base) form. He/she would hold that understanding based on, among other things, the principle that weakly acidic and basic forms of amines are in equilibrium in the body. That principle is reflected in the Henderson-Hasselbalch equation and analogous equations for diprotic acids,

which can be utilized to calculate the respective amounts of protonated and free base forms based on the dissociation constants ( $pK_{as}$ )<sup>1</sup> for the compounds and the pH.

7/9/07

Date



Eric V. Anslyn, Ph.D.

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<sup>1</sup> See page BOE00075146 of BOE00075129-62 for information about the dissociation constants for the protonated forms of pramipexole.