APPENDIX A

Disputed Contentions	Previous Disclosure
Contention: Neither MIRCERA nor epoetin beta are "non-naturally occurring" because glycosylation does not differ from naturally occurring human EPO such as urinary EPO. Located: Imperiali Expert Report at ¶¶ 73-115; Flavell Expert Report at ¶¶ 149-59.	In its Third Supplemental Response to Interrogatory No. 2 of Amgen's First Set of Interrogatories (Nos. 1-15), dated April 2, 2007, Roche stated that, "Neither MIRCERA nor the drug substance RO0503821 is the equivalent of a 'non-naturally occurring glycoprotein product of the expression in a mammalian host cell.'" In addition, Roche's BLA for MIRCERA provides an analysis of carbohydrate structures of epoetin beta. The BLA states that "All structures could be characterized by these methods and correspond to the carbohydrate structures reported for EPO produced recombinantly in CHO cells and also in EPO isolated from human urine . . . The results of this carbohydrate analysis corresponds to data found in the literature for human urinary EPO as well as in EPO obtained by recombinant expression in CHO cells." ITC-R-BLA-00005670-74. See also ITC-R-BLA-00004024-6253. Roche also produced on January 29, 2007, the complete European regulatory filing for NeoRecormon, including extensive information on the production and characterization of epoetin beta . See also ¶ 44 of Roche's Answer and Counterclaims filed November 6, 2006 for further notice and discussion of G.I. Patent 411,678 which describes rEPO and uEPO as being the same. This issue is also addressed by Amgen itself in its Dr. Lodish Expert Report. See Lodish Expert Report ¶ 123 (dated April 6, 2007).
Contention: MIRCERA is materially changed because it has lost a single positive charge with the conversion of an amine to an amide. Located: Klibanov Expert Report at ¶¶ 130-21, 135, 137, 236-37.	In its Third Supplemental Response to Interrogatory No. 3 of Amgen's First Set of Interrogatories (Nos. 1-15), dated April 2, 2007, Roche stated that the drug substance RO0503821 present in all MIRCERA formulations has been materially changed in terms of structure and properties because

	MIRCERA has "different pI (isolectric point) as measured by 2D gel electrophoresis and different overall net ionic charge distribution at blood plasma pH." Additionally, Amgen expert Dr. Katre in her April 6, 2007 opening expert report discusses this very issue which Amgen claims it was surprised to hear about on May 11, stating, "The change of amine to an amide reduces the positive charge on the protein at the site of pegylation. This reduction of one positive charge for the protein will alter the pI and the pKa of the protein which correlate with the charges on the protein." Amgen received substantial discovery on this loss of charge with conversion from an amine to an amide issue, including in Roche's BLA. For example, the BLA states that "The production of RO0503821 includes a pegylation step of EPO with the MSBA30K PEG reagent. This pegylation is the result of the reaction of the succinimidyl ester group of the MSBA30K PEG reagent with the free amino group of the EPO forming an amide bond." ITC-R-BLA-00004235. Changes due to the chemical reaction are also extensively discussed throughout the Chemistry, Manufacture and Control section of the MIRCERA BLA.
Contention: MIRCERA is materially changed because it has a different carbohydrate composition than EPO. Located: Klibanov Expert Report at ¶¶ 150-52.	In its Third Supplemental Response to Interrogatory No. 3 of Amgen's First Set of Interrogatories (Nos. 1-15), dated April 2, 2007, Roche stated that the drug substance RO0503821 present in all MIRCERA formulations has been materially changed in terms of structure and properties because MIRCERA has a "different glycosylation pattern." Also, Roche's BLA describes the changes to the starting EPO as a result of the manufacturing process of EPO; for example, changes to Sialic Acid Content (ITC-R-BLA-00004241-46); N-Linked Glycosylation (ITC-R-BLA-00004247-56); and O-Linked Glycosylation (ITC-R-BLA-

	00004257-68). This issue is also addressed by Amgen itself in its Dr. Lodish Expert Report. See Lodish Expert Report ¶¶ 98 and 172 (dated April 6, 2007).
Contention: MIRCERA does not infringe Amgen's claims because it is not an obligate glycoprotein. Located: Flavell Expert Report at ¶¶ 165-79; Imperiali Expert Report at ¶¶ 112-44, 155-61, 163, 166, 169, 173, 178-82, 190; Cords Expert Report at ¶¶ 1-33.	In its Third Supplemental Response to Interrogatory No. 3 of Amgen's First Set of Interrogatories (Nos. 1-15), dated April 2, 2007, Roche stated that the drug substance RO0503821 present in all MIRCERA formulations has been materially changed in terms of structure and properties because, "it does not require glycosylation to stimulate *in vivo* erythropoietic activity." An obligate protein needs to be properly glycosylated to be active.
Contention: MIRCERA does not infringe because it is not made from cells that are "transformed or transfected with isolated EPO DNA" because protoplast fusion was used to introduce such DNA into Roche's cells. Located: Flavell Expert Report at ¶¶ 61-75.	In its Third Supplemental Response to Interrogatory No. 2 of Amgen's First Set of Interrogatories (Nos. 1-15), dated April 2, 2007, Roche stated that claim 1 of the '868 patent will neither be literally infringed, nor infringed under the doctrine of equivalents, nor directly infringed, nor indirectly infringed by the manufacture, importation, offer for sale, sale, and/or use of MIRCERA in the U.S. after FDA approval because "neither MIRCERA nor the drug substance RO0503821 is produced from 'mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin' as that phrase is properly construed according to the '868 patent specification." Amgen was provided discovery directly on point to this issue. For example, Roche's BLA describes "Transformation and Amplification of EPO Sequences in CHO Cells" (ITC-R-BLA-00004989 -5018), specifically disclosing that "Plasmid DN2-3 was introduced into CHO DHFR deficient DUKX-B11 cells **by protoplast fusion**". (emphasis added). Id. at ITC-R-BLA-00004989. The discussion includes at least one scientific reference that discloses the characteristics of protoplast fusion. See "High-Frequencey Transfer of

	Cloned Herpes Simplex Virus Type 1 Sequences to Mammalian Cells by Protoplast Fusion" at ITC-R-BLA-00005009. Amgen also took the deposition of a Roche 30(b)(6) witness on Roche's cell line, and asked questions relating to transfection. Stern Dep. trans. (3/22/07) at 37. This issue is also addressed by Amgen itself in its Dr. Lodish Expert Report. See Lodish Expert Report ¶¶ 159-60 (dated April 6, 2007).
Contention: MIRCERA is not a pharmaceutical composition of claim 1 of the '422 Patent because it contains more than a single "diluent, adjuvant or carrier." Located: Klibanov Expert Report at ¶¶ 248-30, 261.	In its Third Supplemental Response to Interrogatory No. 2 of Amgen's First Set of Interrogatories (Nos. 1-15), dated April 2, 2007, Roche stated that "neither MIRCERA nor the drug substance RO0503821 meets the properly construed limitation of having 'pharmaceutically acceptable diluent, adjuvant or carrier.'" See also, ITC-R-BLA-00002809; ITC-R-BLA-00004024-6253; ITC-R-BLA-00003365-3397. This issue is also addressed by Amgen itself in its Dr. Lodish Expert Report. See Lodish Expert Report ¶ 92 (dated April 6, 2007).
Contention: MIRCERA is materially changed because Amgen's pegylation program and statements to the PTO show pegylation is unpredictable. Located: Klibanov Expert Report at ¶¶ 174-93; Longmore Expert Report at ¶¶ 88-92.	Amgen's own fact witnesses specifically testified about the unpredictability of pegylation in the fact discovery period prior to submission of any expert reports See, e.g., Lin Dep. trans. (3/28/07) at 100:9-22; Boone Dep. Trans. (3/30/07) at 46:10-22; Elliott Dep. Trans. (3/29/07) at 198:12 - 199:11. Roche also asked for this information directly in a motion to compel Amgen to produce this information. [Doc. No. 331] (dated March 23, 2007). This issue is also addressed by Amgen itself in two separate Expert Reports. See Katre Expert Report ¶¶ 30-40 (dated April 6, 2007); and Torchilin Expert Report ¶¶ 77-96 (dated April 6, 2007).
Contention: MIRCERA is materially changed because it was patented by Roche	Amgen was provided extensive discovery on Roche's patent covering CERA, U.S.

and that it is not an equivalent because it is patented. Located: Klibanov Expert Report at ¶¶ 208-21; Jorgensen Expert Report at ¶¶ 63 fn. 9; Imperiali Expert Report at ¶¶ 164, 172; Longmore Expert Report at ¶ 215; Flavell Expert Report at ¶¶ 144-45.	Patent No. 6,583,272, and was on notice that the patent covered CERA and was significant. *See, e.g.*, deposition of inventor of the '272 patent Pascal Bailon where he states that the '272 patent describes how to make the active ingredient in MIRCERA, RO050-3821 (Bailon Dep. trans. (3/29/07) at 65). Additionally, Amgen's expert Dr. Katre cites both '272 patent and its file history in her opening expert report served on April 6, 2007, belying Amgen's claim that it was surprised on May 11 that the patenting of CERA was a significant issue. Katre Expert Report ¶ 105 (dated April 6, 2007); and Torchilin Expert Report ¶ 70 (dated April 6, 2007). For Amgen to dispute having knowledge of these allegations, Amgen would be acknowledging it was ignorant to the entire history of the development of MIRCERA.[1]
Contention: "Amgen is barred under prosecution history estoppel from asserting equivalents for chemical 'analogs' such as [MIRCERA]." Located: Longmore Expert Report at ¶ 217.	In its Response to Amgen's First Set of Interrogatories (Nos. 1-15), dated January 24, 2007, Roche specifically claimed that Amgen should be estopped from claiming analogs because Amgen surrendered such claims during the prosecution of its own patent.
Contention: MIRCERA "is so changed from EPO in function, way and result, it cannot be found to infringe under the reverse doctrine of equivalents." Located: Flavell Expert Report at ¶¶ 184-88; Longmore Expert Report at ¶¶ 219-22; Klibanov Expert Report at ¶¶ 290-98; Jorgensen Expert Report at ¶ 156; Imperiali Expert Report at ¶¶ 187-93; Mayersohn Expert Report at ¶¶ 155-57.	Amgen never propounded an interrogatory relating to the reverse doctrine of equivalents, so can't complain about lack of detail. This despite Roche including reverse doctrine of equivalents as an affirmative defense as far back as its Answer and Counterclaims filed November 6, 2006. Additionally, in his opening expert report of April 6, 2007 Amgen expert Dr. Lodish acknowledges that he is aware that Roche contends that its manufacturing process, MIRCERA, and its active ingredient do not infringe based on the reverse doctrine of

[1] *See* Klibanov Rebuttal Report ¶¶ at 208-221 (discussing the history of the development of MIRCERA); Imperiali Rebuttal Report at ¶ 172 (the PTO viewed MIRCERA as novel and different from EPO pharmaceutical compositions found in the prior art.).

	equivalents. Lodish Expert Report ¶ 225 (dated April 6, 2007). Amgen was aware reverse doctrine of equivalents was an issue long before it received Roche's May 11 rebuttal expert reports.
Contention: Because Aranesp is more similar to EPO than MIRCERA, and because Aranesp does not infringe, then MIRCERA does not infringe. Located: Klibanov Expert Report at ¶¶ 277-89.	In its First Set of Interrogatories (Nos. 1-12), served December 6, 2006, Roche specifically asked whether the making, using, offering to sell or selling of Aranesp is covered by any or all of the claims of the patents-in-suit, putting Amgen on notice as far back as December that whether or not Aranesp was covered by the patents-in-suit was relevant to Roche's defenses. Defendants' Interrogatory No. 8, Dec. 6, 2006. In its Response to Interrogatory No. 8 of Roche's First Set of Interrogatories (Nos. 1-12), dated January 9, 2007, and its Supplemental Response to Interrogatory No. 8 of Roche's First Set of Interrogatories (Nos. 1-12), dated February 9, 2007, Amgen stated that Aranesp is covered by the claims in suit. Amgen internal docs also show comparisons between CERA and Aranesp, including positioning docs. See Elliott Depo. Exhibits 13, 14; and Molineux Depo. Exhibit 2. Amgen clearly was focused on this issue.