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§ 103 Obviousness	
"The claims of the patents-in-suit are invalid under 35 U.S.C. § 103 because they would have been obvious to one of ordinary skill in the art at the time of the invention. Roche may rely on at least the following prior art, alone or in combination, as rendering the claims of the patents-in-suit obvious" • Fails to define the state of the art and the level of ordinary • Fails to disclose any obviousness-making combinations • Fails to disclose any motivation to combine described • Fails to provide a complete list of alleged prior art references	• For the first time in this case, more than 50 publications, patents, and patent applications referenced, relating to various subjects, including chemical synthesis of DNA and expression of biologically-active EPO in mammalian cells are disclosed • Roche alleges, for the first time in this case, that the invention claimed in the '008 patent were obvious in light of the prior art: o Processes for chemically synthesizing DNA were well-known in the art o Probing methods used by Dr. Lin to obtain the EPO DNA were known in the art o cDNA library obtained from one of several human EPO-producing cell lines offered reasonable likelihood of success in cloning EPO gene • For the first time in this case specific cell lines are disclosed as obvious sources of EPO and EPO mRNA: o Renal carcinoma cell line generated by Fisher o Yolk sac carcinoma cell line studied by Gaylis o Renal carcinoma cell line (RC-1) established by Shouval • Roche alleges that the patents in suit are obvious in light of Miyake and Alton, a combination not previously asserted in this case • For the first time in this case, Roche attempts to rebut the

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	secondary considerations of non-obviousness. Roche asserts: o Long-felt need fulfilled by Dr. Goldwasser's work and the '008 patent o Commercial success attributable to the '008 patent, not the patents-in-suit o Dr. Lin's patents do not describe EPO pure enough for a pharmaceutical composition, so Dr. Lin is not responsible for satisfying long-felt need or commercial success • Seven expert reports address this topic, dedicating over 175 pages exclusively to the invalidity defense of obviousness
§ 102 Anticipation	
"The claims of the '422 and '933 patents (and the '080 patent …) are invalid under 35 U.S.C. § 102 as anticipated by any one of several prior art publications describing use of various sources of EPO, including EPO expressing cells, as well as urine from anemic subjects, for isolating and purifying a therapeutically effective amount of human erythropoietin" • Fails to provide a complete list of prior art • No effort to correlate prior art to asserted claims • Fails to specifically identify the sources, particularly the "EPO expressing cells" • Fails to identify the specific claims allegedly anticipated	• Specific claims allegedly anticipated by urinary EPO prior art identified for the first time in this case: o '933 claims 3, 7, 8, 9, 11, 12, and 14 o '080 claim 3 o '422 claim 1 • Roche argues for the first time that the glycoforms of human erythropoietin expressed in at least some mammalian host cells are all encompassed within the naturally occurring human erythropoietin glycoforms found in human urinary erythropoietin • For the first time in this case, Dr. Essers EPO-rich plasma study is identified as prior art, allegedly anticipating '422 claim 1, as plasma administered to humans increased

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	reticulocyte count • Two expert reports address this topic, dedicating approximately 41 pages (excluding technical background) exclusively to the invalidity defense of anticipation
§ 112 Lack of Written Description and Non-Enablement: Purification	
Nothing Disclosed.	• Roche identifies, for the first time in this case, the following claims of the patents-in-suit that it alleges are not enabled or lack written description of purification techniques sufficient to commercially produce a pharmaceutical composition: o '422 claim 1 o '080 claims 4 and 6 o '933 claims 9, 11, 12, and 14 • Roche alleges for the first time in this case that the patents-in-suit do not adequately describe how to produce sufficient quantities of pure recombinant human erythropoietin for commercial production • Roche alleges for the first time in this case that purification by HPLC C_4, as described in the patents-in-suit, is insufficient to achieve the levels of purity required to make a pharmaceutical composition • Roche alleges for the first time in this case that Amgen had to invent a new procedure for purification (described in the '016 patent) because the method described in the patents-in-suit was insufficient to produce commercial

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	amounts of pure recombinant human erythropoietin • Two expert reports address this topic, dedicating over 20 pages exclusively to the invalidity defense of non-enablement of purification
§ 112 Indefiniteness and Non-Enablement: Non-Naturally Occurring	
Nothing Disclosed.	• Roche alleges for the first time in this case the purported indefiniteness of '933 claim 3 and '080 claim 4 for the use of the phrase "non-naturally occurring" • Roche alleges for the first time in this case that there is no indication in Example 10 of a standard for urinary erythropoietin, both with regard to source and purity, precluding the definition of "non-naturally occurring" • Roche alleges for the first time in this case that errors in the carbohydrate data included in Example 10, prevent one of ordinary skill in the art from distinguishing between naturally- and non-naturally-occurring erythropoietin glycoproteins • One expert report dedicates over five pages of analysis to the invalidity defense of indefiniteness and non-enablement of '933 claim 3 and '080 claim 4
§ 112 Lack of Written Description and Non-Enablement: Units of Erythropoietin	
"It is Roche's contention that the phrase [U of erythropoietin] as used in the claims is indefinite, cannot be properly defined in view of the patent specification and is otherwise scientifically inaccurate, as radioimmunoassay alone cannot measure	• Roche alleges for the first time in this case that '349 claim 7 is not enabled and lacks written description • Roche alleges for the first time in this case that '349 claim

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erythropoietin units ('U') as required by the claim phrase."	7 requires assumptions are purportedly not disclosed in the specification • Roche alleges for the first time in this case that there is no fixed erythropoietin standard upon which one could rely when determining units of erythropoietin by RIA, and that Amgen was purportedly aware of this variation in EPO standards at the time of the inventions • Roche alleges for the first time in this case that the scope of '349 claim 7 is overbroad, as CHO and COS are not representative of the entire group of "vertebrate cells" claimed • Roche alleges for the first time in this case that the technique described in the '349 patent is not predictable for non-mammalian cell lines • Three expert reports address this topic, dedicating approximately 46 pages exclusively to the invalidity defense of non-enablement, lack of written description, and indefiniteness of '349 claim 7
§ 112 Lack of Written Description and Non-Enablement: Pegylated Compounds	
"The asserted claims of the patents-in-suit are invalid for lack of written description and enablement because it is undisputed that there is no written description of the techniques for pegylating proteins within the patent specifications."	• Roche alleges for the first time in this case that purported difficulties associated with generating EPO analogs demonstrate the undue experimentation required to make peg-EPO • Roche alleges for the first time in this case that Amgen

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	could not predict whether protein modifications like pegylation could result in active proteins • Roche alleges for the first time in this case that Amgen had not performed any research on pegylated erythropoietin prior to 1985 • A full expert report, containing 15 pages of analysis, is dedicated exclusively to the invalidity defense of non-enablement of pegylated compounds
§ 102 (f) Inventorship/Derivation	
"The asserted claims of [the '422 and '933 patents] are invalid under 35 U.S.C. § 102(f) as derived from others. In particular, before Amgen's alleged invention of the subject matter of these claims, Dr. Eugene Goldwasser had conceived and reduced to practice a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier." • No mention of tryptic fragments or urinary EPO	• Roche alleges for the first time in this case that the availability of purified human EPO and tryptic fragments provided by Goldwasser were necessary for the cloning of the EPO gene. • Roche asserts for the first time in this case that the claims of the patents-in-suit would have been obvious if Dr. Goldwasser's purified human EPO or tryptic fragments had been available to the public. • One report dedicates four pages exclusively to the topic of Goldwasser's involvement in the patents-in-suit
Obviousness-Type Double Patenting Over '008 Patent	
"The '008 patent and the patents-in-suit all share the same specification and single inventor, and demonstrate that Amgen possessed only a single invention with minor obvious variations" • Specific claims of '008 rendering claims-in-suit obvious	• Roche alleges, for the first time in this case, that at least claims 2, 4, 6, 12, 25, and 27 of the '008 patent render the following claims of the patents-in-suit obvious: o '868 claims 1 and 2 o '698 claims 4, 5, 6, 7, 8, and 9

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not identified • Specific claims of patents-in-suit rendered obvious by '016 not identified • Level of ordinary skill not identified	o '349 claim 7 o '422 claim 1 o '933 claims 3, 7, 8, 9, 11, 12, and 14 o '080 claims 3, 4, and 6 • Roche alleges for the first time in this case that once a skilled worker possessed the EPO DNA claimed in the '008 patent, it would have been obvious to express the glycosylated recombinant protein in any one of a number of widely-available mammalian host cell expression systems, including CHO and COS • Roche alleges for the first time in this case that the process claims of the '868, '698, and '349 patents recite the intended use of the DNA and host cells claimed by the '008 patent • Roche alleges for the first time in this case that the pharmaceutical composition claims are obvious over the '008 claims as there purportedly was nothing non-inventive about the use of diluents, adjuvants, and carriers • Four expert reports address this topic, dedicating over 50 pages exclusively to the invalidity defense of obviousness-type double patenting over the '008 patent
Obviousness-Type Double Patenting Over '016 Patent	
"The claims of the '868, '933, '698, '080, '349 and '422 patents are invalid for double patenting over claims of Amgen's earlier issued and now expired U.S. Patent No. 4,703,008 ('the '008	• Roche alleges for the first time in this case that the following claims of the patents-in-suit that it alleges are

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patent') and U.S. Patent No. 4,667,016" • Specific claims of '016 rendering claims-in-suit obvious not identified • Specific claims of patents-in-suit rendered obvious by '016 not identified	obvious over claim 10 of the '016 patent: o '933 claims 3, 7, 8, 9, 12, 11 and 14 o '080 claims 3, 4, and 6 o '422 claim 1 o '698 claims 4, 5, 6, 7, 8, and 9 o '868 claims 1 and 2 o '349 claim 7 • Roche alleges for the first time in this case that the process for recovering purified recombinant EPO described in the '016 patent renders the patents-in-suit obvious, as all of the elements of the claims listed above are either found within '016 claim 10 or would be obvious to one of ordinary skill in the art at the time the inventions were made • 15 pages of one expert report are dedicated exclusively to the invalidity defense of obviousness-type double patenting over the '016 patent
Inequitable Conduct	
Roche asserts numerous inequitable conduct allegations, outlined in its [Proposed] Amended Answer – Seventh Affirmative Defense and its response to Amgen's Interrogatory No. 26. • Fails to provide a complete list of alleged failures to disclose and misrepresentations	• Roche alleges for the first time in this case that Amgen failed to disclose to the PTO previously unasserted publications, declarations, and patents that should have been considered as prior art • Roche alleges for the first time in this case that Amgen failed to disclose to the PTO their work with the 1411 human tumor cell line and the Baron-Goldwasser experiment

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	• Roche alleges for the first time in this case that Amgen misrepresented to the PTO that a two-way obviousness test applied in overcoming the Lai patent • Roche alleges for the first time in this case that Amgen concealed the standard used in RIA from the examiner during prosecution of the '349 patent • An entire expert report describing PTO practice and procedure, consisting of over 200 pages, is dedicated to the unenforceability defense of inequitable conduct