

EXHIBIT A-3

Invalidity Claim Chart of Lam, alone or in combination with any of Sigg, Boulange, Reuter, Scypinski, Nema, D'Souza, Furfine, Badkar, Macugen, Eylea, Lucentis, Stewart, USP789, Liu, Hioki, DC365, Khandke, against U.S. Patent No. 9,220,631.

Charted Reference:

PCT Patent Publication No. WO 2008/077155 to Lam *et al.* ("Lam"), in view of Sigg, Boulange, Reuter, Scypinski, Nema, D'Souza, Furfine, Badkar, Macugen, Eylea, Lucentis, Stewart, USP789, Liu, Hioki, DC365, Khandke, and obvious claims 1-26 of U.S. Patent No. 9,220,631.

This claim chart is based on Regeneron's current understanding of the asserted claims, and Regeneron's investigation. Regeneron is not admitting to the accuracy of any particular construction. Regeneron reserves all rights to amend this claim chart in light of any claim construction developments or any amendments to Novartis's infringement contentions. Regeneron's contentions, should such developments occur or amendments be allowed. Further, as discovery is ongoing and Regeneron seeks discovery from third parties regarding the references identified in Regeneron's invalidity contentions as well as prior art, Regeneron reserves the right to revise its invalidity contentions as appropriate in view of any ongoing developments.

The claim chart below identifies where each limitation of each asserted claim of the 631 Patent can be found in the references provided below are exemplary, rather than exhaustive, and Regeneron reserves the right to rely upon any other prior art references. Where Regeneron identifies a portion of a reference's text, the identification should be understood as corresponding to a figure or diagram, and vice versa.

Claim Language	Corresponding Disclosure
<p>[1.a-pre] A pre-filled, terminally sterilized syringe for intravitreal injection</p>	<p>Lam discloses a pre-filled, terminally sterilized syringe for intravitreal injection</p> <p>For example, see the following passages and/or figures, as well as all related d</p> <p>Objects used in medical applications are generally sterilized before use. St be accomplished by a variety of methods including, e.g., steam sterilization sterilization, gas sterilization (e.g. with ethylene oxide), and chemical ster However, these treatments cannot be used for objects containing pharmaco compositions because their active ingredients are typically sensitive to the steam and gas sterilization are generally performed at high temperatures (a to 55 0 C or higher) that damage certain active ingredients in pharmaceuti compositions. Similarly, the agents used for radiation or chemical steriliza cause chemical damage to the active ingredients. Consequently, pharmace compositions are generally sterilized by an alternative method, e.g. by filtr packaged into separately sterilized objects. Because of the complexity of t difficult to also ensure the sterility of the surfaces of the objects.</p> <p>In many circumstances it would be advantageous to sterilize the surfaces o in order to reduce the risk of contamination during subsequent handling. F there is an increased risk of endophthalmitis after intraocular injection if th syringe used for injection is not sterilized. Thus, there remains a need for c cost-effective methods of surface-sterilizing objects containing ethylene-o temperature-sensitive compounds, such as biological molecules, without a adverse effect on their activity or integrity.</p> <p>Lam at 1:14-32.</p> <p>The invention relates to methods for surface-sterilizing objects containing oxide-sensitive, temperature-sensitive compounds, such as biological mol invention is based, in part, on the surprising discovery of ethylene-oxide - sterilization conditions that will effectively sterilize the surface of an obje</p>

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	<p>not significantly damage ethylene-oxide-sensitive, temperature-sensitive compound contained inside.</p> <p>In one aspect, the invention provides a method for surface-sterilizing an object in an ethylene-oxide(EtO)-impermeable interior space containing a compound with temperature-sensitive and EtO-sensitive activity by exposing the object to conditions such that the object is surface-sterilized and the compound retains at least 90% of said activity. In some embodiments, the conditions comprise: a) temperature between 25 0 C and 35 0 C; b) EtO concentration of between 300 mg/L and 800 mg/L; and c) relative humidity between 45% and 60%; for between 1 and 6 hours. In some other embodiments, the conditions comprise: a) temperature between 27 0 C and 30 0 C; b) EtO concentration of between 300 mg/L and 600 mg/L; and c) relative humidity between 45% and 52%; for between 1 and 6 hours. In some other embodiments, the conditions comprise: a) temperature of 30 0 C; b) EtO concentration of 600 mg/L; and c) relative humidity of 50%; for 1, 1.5 or 2 hours.</p> <p>In some embodiments, the compound retains at least 90% of said activity. In some other embodiments, the compound is a polypeptide, e.g. an antibody, which includes monoclonal antibodies, chimeric antibodies, humanized antibodies or human antibodies. In some embodiments where the compound is a polypeptide, the percent of active polypeptide is not statistically different from a control polypeptide not exposed to EtO. In some embodiments, the antibody is an antigen-binding fragment, e.g. a Fab fragment. In some embodiments, the Fab fragment binds VEGF, e.g. ranibizumab (Lucentis). In some other embodiments, the compound is present in an aqueous pharmaceutical composition, e.g. a composition comprising at least one of: an amino acid, a disaccharide, a surfactant, or an ionic surfactant. In some embodiments the pharmaceutical composition comprises histidine, trehalose and polysorbate 20.</p> <p>In some embodiments, the object is a syringe. In some embodiments the syringe comprises glass and comprises a stopper comprising D777-7 laminated with FluoroTec® and a tip cap comprising D777-7 laminated with FluoroTec® or D21-7H laminated with FluoroTec®.</p>

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	<p>FluroTec®. In some embodiments, the object is contained within a package made of an ethylene oxide (EtO)-permeable material, e.g. TYVEK®.</p> <p>Lam at 2:3-33.</p> <p>In some embodiments, the pharmaceutical composition is designed for intramuscular injection.</p> <p>Lam at 11:30-31.</p> <p>The methods of the invention are typically used to sterilize objects containing pharmaceutical formulations. For example, the methods of the invention may be used to sterilize syringes, vials or cartridges (such as are used in devices designed for multiple use). In addition, the method of the invention may be used with a syringe with a needle. In the latter case, some sort of cap or needle shield is generally provided. The needle will subsequently be attached. The following example is intended to illustrate the practice of the present invention and is not provided by way of limitation. The disclosures of all patent and scientific literatures cited herein are expressly incorporated in their entirety by reference.</p> <p>Lam at 12:31-13:6.</p> <p>We performed experiments to identify whether there were parameters for sterilization that would effectively sterilize the surface of an object but which do not damage an ethylene-oxide-sensitive, temperature-sensitive compound contained inside. We performed EtO sterilization runs on syringes containing a ranibizumab solution at a protein concentration indicated in Table 2 in a solution with 10 mM histidine, 10 mM α - trehalose dehydrate, 0.01% polysorbate 20, pH 5.5) where each run had the following standard EtO sterilization steps: (1) set temperature; (2) evacuate chamber to about 5.0" HgA; (3) leak test; (4) wash twice with nitrogen; (5) humidify chamber and incubate for about 30 min; (6) inject EtO gas and incubate for dwell time; (7) evacuate chamber to about 5.0" HgA; and (8) wash four times with nitrogen (each wash cycle i</p>

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	<p>min). In addition to the syringe, each run also included a paper strip with a 1.9×10^6 Bacillus subtilis spores, which was used to monitor the sterilization. The strip was soaked in media, vortexed vigorously and then serial dilution and grown for one week. We then varied the following sterilization-critical parameters indicated in Table 1 : temperature, relative humidity, time of exposure (gas), and EtO concentration</p> <p>Lam at 13:12-26.</p> <p>We also tested several different syringe components: where the stopper on the syringe comprised D777-7 laminated with a 125 μm coating of FluroTec® barrier film, the tip cap comprised either D777-7 or D21-7H laminated on both the surface with the tip of the syringe and the exterior surface with a 125 μm coating of FluroTec® barrier film (all components from West Pharmaceutical Services / Daikyo). We measured the residual EtO in the syringe and the stability of ranibizumab for 30 days as the treatment and at various monthly time points thereafter. For IEC, we measured the percentage of protein in the main peak and in the acidic and basic peaks. The percentage of protein in the basic peak representative of alkylation which may have been caused by EtO treatment. As shown in Table 3, under all conditions tested the percentage of protein in the basic peaks was at most approximately 1% over control. Further, when FluroTec® barrier film was used on the syringe components, the percentage of protein in the basic peak was not statistically different from control.</p> <p>Lam at 15:12-24.</p>

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