

EXHIBIT A-1

Invalidity Claim Chart of Sigg, alone or in combination with any of Boulange, Lam, Reuter, Scypinski, M Schoenknecht, Chacornac, Nema, D'Souza, Furfine, Badkar, Macugen, Eylea, Lucentis, Stewart, USP789 Hagen, Khandke, Wittland, Shams, Dixon, and/or Cormier against U.S. Patent No. 9,220,

Charted Reference:

PCT Patent Publication No. WO 2011/006877 to Sigg *et al.* (“Sigg”), alone or in view of Boulange, Lam, Reuter, Shah, Fries, Schoenknecht, Chacornac, Nema, D'Souza, Furfine, Badkar, Macugen, Eylea, Lucentis, Stewart, US DC365, Hagen, Khandke, Wittland, Shams, Dixon, and/or Cormier, render obvious claims 1-26 of U.S. Patent No.

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 discovery.

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 the corresponding 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>Sigg 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>Terminal sterilization of prefilled containers in secondary packaging is on the device to an end user with a low bio-burden and low risk of contamination application of the product by the end user. Moreover there is a strong market for terminally antimicrobially-treated medical devices, such as prefilled syring, intravitreal injections.</p> <p>Sigg at 2:15-19.</p> <p>Described herein is a terminal sterilization and surface decontamination tr prefilled containers, specifically for sterilization of prefilled containers con sensitive solutions, such as a drug product or biological therapeutic, within packaging. In one embodiment, terminal sterilization is achieved by treating containers within secondary packaging with controllable vaporized-hydrog (VHP).</p> <p>Sigg at 3:8-13.</p> <p>The method and system described herein decontaminate or, more preferably, an outside surface of primary packaged drug products within a secondary improving safety of products for critical administration (e.g. use in a surgic intravitreal injections)</p> <p>Sigg at 4:12-15.</p> <p>In one embodiment, the prefilled container is a syringe. Other suitable pre include vials, bottles, bags and other medical devices capable of containin solution or a solution requiring sterilization.</p>

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	<p>In one embodiment, the syringe is filled with a drug product, such as in the form of a solution, powder or solid. In another embodiment the drug product is a solid drug solution or protein solution that is otherwise sensitive to exposure to high temperatures, such as those used in steam sterilization, and ionizing energy such as gamma or beta rays and oxidizing gasses. In yet another embodiment the drug product is one that has been lyophilized, in other words a solid, and requires reconstitution in water or solution prior to use.</p> <p>In another embodiment, a solution is any drug product having requirements for sterility of the drug product container surface. In one particular embodiment the drug product is a protein solution, such as ranibizumab (e.g. 6mg/ml or 10 mg/ml) for intravitreal injection.</p> <p>Sigg at 9:1-14.</p> <p>Example 1</p> <p>In the following experiment, prefilled syringes were treated with a vaporized hydrogen peroxide sterilization treatment in a chamber, either by a single pass through the sterilization procedure or two passes (shown in the table below as 2 x) through the sterilization procedure. Syringes containing protein solutions treated by VHP were compared to control syringes treated with VHP to determine if the integrity of the protein present in solution was maintained.</p> <p>A formulation as described in U.S. Patent No. 7,060,269 was tested for protein degradation following treatment by VHP.</p> <p>Approximately 10 mL of solution was filtered through a 0.22 µm syringe filter (GV filter available from Millipore, Billerica, MA USA.) Filling of 0.5 mL was performed in a sterile lab for hydrogen peroxide treatment.</p>

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	<p data-bbox="678 709 1624 814">Analysis after the treatment with VHP revealed the following protein content by HPLC analysis: byproducts and degradation products by HPLC (IEC) and degradation products by HPLC (SEC).</p> <p data-bbox="766 861 1318 886">Table 1: Protein Stability Following Treatment with VHP</p> <table border="1" data-bbox="756 898 1624 1121"> <thead> <tr> <th>Batch</th> <th>IEC (% main peak)</th> <th>IEC (% basic peak)</th> <th>SEC (% r</th> </tr> </thead> <tbody> <tr> <td>Control</td> <td></td> <td></td> <td></td> </tr> <tr> <td>9823.01 CSi</td> <td>98</td> <td>2</td> <td>1</td> </tr> <tr> <td>9823.02 CSi</td> <td>98</td> <td>2</td> <td>1</td> </tr> <tr> <td>1 x treatment</td> <td></td> <td></td> <td></td> </tr> <tr> <td>9823.04 CSi</td> <td>98</td> <td>2</td> <td>1</td> </tr> </tbody> </table> <table border="1" data-bbox="756 1171 1624 1360"> <tbody> <tr> <td>9823.05 CSi</td> <td>98</td> <td>2</td> <td>1</td> </tr> <tr> <td>2 x treatment</td> <td></td> <td></td> <td></td> </tr> <tr> <td>9823.07</td> <td>98</td> <td>2</td> <td>1</td> </tr> <tr> <td>9823.08</td> <td>98</td> <td>2</td> <td>1</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p data-bbox="678 1423 1624 1780">The results seen were within the requirement; there were no differences between results of the untreated syringes and with hydrogen-peroxide treated syringes. Analysis can also be carried out at different time points following treatment, such as one month, three months and six months following treatment by VHP, or over the shelf-life of the prefilled container. Analysis can be carried out to determine continued stability of the protein solution, including tests by HPLC for presence of by-products and degradation products by HPLC laboratory protocols. Analysis can also be carried out by the presence of hydrogen peroxide changes, such as measuring the concentration of H₂O₂ in solution by a fluorescence assay using an over-the-counter commercially available kit in conjunction with a fluorimeter with fluorescence detection.</p> <p data-bbox="620 1822 893 1856">Sigg at 20:10-21:11.</p>	Batch	IEC (% main peak)	IEC (% basic peak)	SEC (% r	Control				9823.01 CSi	98	2	1	9823.02 CSi	98	2	1	1 x treatment				9823.04 CSi	98	2	1	9823.05 CSi	98	2	1	2 x treatment				9823.07	98	2	1	9823.08	98	2	1				
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	<p>To the extent Novartis alleges this limitation is not met by any of the disclosures, it would have been obvious in view of Boulange, Lam, Reuter, Scypinski, Metzger, Schoenknecht, Chacornac, Nema, D’Souza, Furfine, Badkar, Macugen, Eylea, USP789, Liu, Hioki, DC365, Hagen, Khandke, Wittland, Shams, Dixon, and/or Exhibits A-2–A-13, B-1–B-3 and all references cited therein.</p>										
<p>[1.b] the syringe comprising a glass body forming a barrel, a stopper and a plunger</p>	<p>Sigg discloses the syringe comprising a glass body forming a barrel, a stopper and a plunger.</p> <p>For example, see the following passages and/or figures, as well as all related disclosures.</p> <p>Further, sterilizing doses of gamma rays cause a brown discoloration of glass, the device, and is prone to damage elastomeric materials like plunger stoppers. The destruction of the elastomers leads to increased stickiness of the components, impairing the functionality of the system. Thus radiation is not an appropriate method for sterilizing prefilled containers, such as syringes, containing a biotech drug.</p> <p>Sigg at 2:1-6.</p> <p>Additionally, the oxidative stress exerted on a 0.5% Polysorbate 20 solution in glass syringes (1 mL long, ISO) was investigated by measurement of peroxide levels according to standard protocols. The total amount of peroxides was measured by the Peroxide Oxidation (FOX) test, according to a standard protocol.</p> <p>Table 3: Peroxide Levels Following Beta Irradiation of Prefilled Containers</p> <table border="1" data-bbox="792 1560 1624 1791"> <thead> <tr> <th data-bbox="792 1560 1214 1633">Number of passes through E-beam tunnel</th> <th data-bbox="1214 1560 1624 1633">Peroxide content of 0.5% Polysorbate 20 solution in water in 1mL long glass syringe (ISO) [μg/mL]</th> </tr> </thead> <tbody> <tr> <td data-bbox="792 1633 1214 1675">Reference (not treated)</td> <td data-bbox="1214 1633 1624 1675">0.04</td> </tr> <tr> <td data-bbox="792 1675 1214 1707">1 pass</td> <td data-bbox="1214 1675 1624 1707">0.04</td> </tr> <tr> <td data-bbox="792 1707 1214 1749">3 passes</td> <td data-bbox="1214 1707 1624 1749">0.03</td> </tr> <tr> <td data-bbox="792 1749 1214 1791">5 passes</td> <td data-bbox="1214 1749 1624 1791">0.05</td> </tr> </tbody> </table>	Number of passes through E-beam tunnel	Peroxide content of 0.5% Polysorbate 20 solution in water in 1mL long glass syringe (ISO) [μ g/mL]	Reference (not treated)	0.04	1 pass	0.04	3 passes	0.03	5 passes	0.05
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