

EXHIBIT A-4

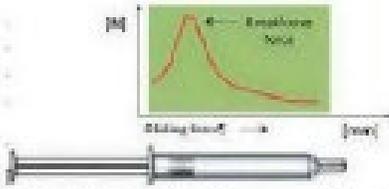
Invalidity Claim Chart of Reuter, alone or in combination with any of Sigg, Boulange, Lam, Scypinski, Metzner, Fries, Schoenknecht, Chacornac, Nema, D'Souza, Furfine, Badkar, Macugen, Eylea, Lucentis, Stewart, USP789, Liu, Hioki, DC365, Hagen, Khandke, Wittland, Shams, Dixon, and/or Cormier against U.S. Patent No. 9,220,631.

Charted Reference:

Bruno Reuter and Claudia Petersen. "Die Silikonisierung von Spritzen: Trends, Methoden, Analyseverfahren," *Pharmazie* (2012): 238-244. ("Reuter"), alone or in view of Sigg, Boulange, Lam, Scypinski, Metzner, Shah, Fries, Schoenknecht, Chacornac, Nema, D'Souza, Furfine, Badkar, Macugen, Eylea, Lucentis, Stewart, USP789, Liu, Hioki, DC365, Hagen, Khandke, Wittland, Shams, Dixon, and/or Cormier, render 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 of the prior art. 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 or Regeneron's invalidity 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 the 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 prior art. 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 ... syringe</p>	<p>Reuter discloses a “pre-filled syringe.”</p> <p>For example, see the following passages and/or figures, as well as all related d</p> <p>Ready-to-fill, i.e. sterile, prefillable glass syringes, are washed, siliconized and packaged by the primary packaging manufacturer. They can then be filled by pharmaceutical companies without any further processing. These days the prefillable syringes are made of glass and the trend looks set to continue.</p> <p>Reuter at 1.</p> <p>Although syringes and cartridges are always siliconized, this applies to a large number of vials and ampoules. On the container the siliconization provides a barrier between the glass and drug formulation. It also prevents the adsorption or formation of components on the glass surface. The hydrophobic deactivation of the surface improves the containers' drainability. In prefillable syringes and cartridges siliconization also performs another function. It lubricates the syringe barrel or cartridge so that the plunger to glide through it. Siliconization of the plunger stopper alone does not provide adequate lubrication.</p> <p>Reuter at 1.</p>  <p>Fig. 3: Extrusion force profile of a prefillable syringe.</p> <p>Reuter at 3.</p>

Claim Language	Corresponding Disclosure
	<p>Prefillable glass syringes are only manufactured from high quality type 1 glass.</p> <p>Reuter at 3.</p> <p>To the extent Novartis alleges this limitation is not met by any of the disclosures have been obvious in view of Sigg, Boulange, Lam, Scypinski, Metzner, Shah, Schoenknecht, Chacornac, Nema, D’Souza, Furfine, Badkar, Macugen, Eylea, USP789, Liu, Hioki, DC365, Hagen, Khandke, Wittland, Shams, Dixon, and/or Exhibits A-1–A-3, A-5–A-13, B-1–B-3 and all references cited therein.</p>
<p>[1.a-pre] A ... terminally sterilized syringe</p>	<p>Reuter discloses the need to terminally sterilize the syringe. It would have been POSITA to terminally sterilize the prefilled syringes disclosed in Reuter to ensure when administered to a patient.</p> <p>For example, see the following passages and/or figures, as well as all related disclosures:</p> <p>Ready-to-fill, i.e. sterile, prefillable glass syringes, are washed, siliconized and packaged by the primary packaging manufacturer. They can then be filled by pharmaceutical companies without any further processing. These days the prefilled syringes are made of glass and the trend looks set to continue. The siliconization of the syringe barrel is an extremely important aspect of the sterile, pre fillable glass syringes because the functional interaction of the siliconization and the plunger stopper siliconization is crucial to the efficiency of the entire system.</p> <p>Reuter at 1.</p> <p>A POSITA would have understood the need to terminally sterilize the claimed syringe. It would have had a reasonable expectation of success combining Reuter and Larsson, Metzner, Wittland, Hagen, Scypinski, and/or D’Souza in a way that satisfies the</p>

Claim Language	Corresponding Disclosure
	<p>To the extent this limitation is not expressly and/or inherently disclosed by Reuter, it would have been obvious, even without resorting to the disclosures of any other references, that it was within the common knowledge of persons of ordinary skill in the art, and that one of ordinary skill would be able to apply, according to known methods, to achieve predictable results.</p> <p>In addition, the 631 Patent fails to disclose a new process for terminal sterilization. The 631 Patent explains “a careful balancing act is required to ensure that while a suitable level of sterilization is carried out, the syringe remains suitably sealed, such that the therapeutic is not lost.” 631 Patent at 1:31-36. The 631 Patent says that the sterilization it discloses may be carried out by various methods, such as by using VHP or EtO, but no details are provided regarding the specific steps of the process itself. 631 Patent at 9:49-54 (“As noted above, a terminal sterilisation process may be used to sterilise the syringe and such a process may use a known process such as an ethylene oxide (EtO) or a hydrogen peroxide (H2O2) sterilisation process. Needles to be used in the syringe may be sterilised by the same method, as may kits according to the invention.”). The description in the 631 Patent only sets forth desired results – how long the syringe should be sterilized, the Sterility Assurance Level, the alkylation of the product, and the amount of product remaining – but does not detail the steps to achieving them. <i>See e.g., id.</i> at 9:55-56. The 631 Patent does not provide any details regarding the known sterilization methods, and those methods were known in the art and thus render this claim limitation obvious.</p> <p>A POSITA would have known that terminal sterilization of prefilled containers and syringes in primary packaging is one way to sterilize the device and maintain a low bio-burden and reduce the number of contaminants. A POSITA also would have known that terminal sterilization is achieved through a range of solutions, including those that are temperature, oxidation, or radiation based.</p> <p>Moreover, if Novartis contends that Reuter does not disclose the claimed limitation, it renders this limitation obvious in view of numerous prior art references. A person of ordinary skill in the art would have been motivated to combine the teachings of Reuter with those of Metzner, Wittland, Hagen, Scypinski, and/or D’Souza, and would have had a reasonable expectation of success in doing so, at least because these references are in the same field of endeavor. Moreover, the references teach the benefits and advantages of applying terminal sterilization techniques, as can be seen in the excerpts below. It further would have been an</p>

Claim Language	Corresponding Disclosure
	<p>choice. Such a person likewise would have understood that such combination was nothing more than a simple substitution or combination of known elements and application of known techniques, to achieve predictable results.</p> <p>For example, see the following passages and/or figures, as well as all related disclosures.</p> <p>Objects used in medical applications are generally sterilized before use. Sterilization can be accomplished by a variety of methods including, e.g., steam sterilization, autoclave sterilization, gas sterilization (e.g. with ethylene oxide), and chemical sterilization. However, these treatments cannot be used for objects containing pharmaceutical compositions because their active ingredients are typically sensitive to the conditions of steam and gas sterilization. Steam and gas sterilization are generally performed at high temperatures (at least 121°C or higher) that damage certain active ingredients in pharmaceutical compositions. Similarly, the agents used for radiation or chemical sterilization generally cause damage to the active ingredients. Consequently, pharmaceutical compositions are generally sterilized by an alternative method, e.g. by filtration, and then packaged in separately sterilized objects. Because of the complexity of this process, it is 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 of the objects in order to reduce the risk of contamination during subsequent handling. For example, there is an increased risk of endophthalmitis after intraocular injection if the syringe used for injection is not sterilized. Thus, there remains a need for a simple, cost-effective method of surface-sterilizing objects containing ethylene-oxide-sensitive, temperature-sensitive compounds, such as biological molecules, without an 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 ethylene-oxide-sensitive, temperature-sensitive compounds, such as biological molecules. The invention is based, in part, on the surprising discovery of ethylene-oxide-b</p>

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.