CASE PAT053689-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Sigg, Juergen

Art Unit: 41424142
Examiner: SPAMER, DONALD ROBERT

INTERNATIONAL APPLICATION NO: PCT/EP2010/060011
FILED: July 13, 2010
U.S. APPLICATION NO: 13/382380
35 USC §371 DATE: January 05, 2012
FOR: Surface Decontamination of Prefilled Containers in Secondary Packaging

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JUERGEN SIGG, Ph.D.

I, Juergen Sigg, declare and say that:

1. I reside at Karl-Arzet-Weg 25, Loerrach, Germany.

2. I am employed by Novartis Pharma AG ("Novartis"), located at Fabrikstrasse, Basel, Switzerland. I have been so employed since 1992. My title is Principal Fellow. In this position, which I have held since 2006, I am responsible for development, transfer and validation of pharmaceutical formulations and manufacturing processes of biotechnically derived pharmaceutical drug products.

3. I received a Ph.D. degree in Pharmaceutical Technology from University of Regensburg in Regensburg (Germany) in 1991.

4. I am the sole inventor of the invention claimed in pending patent application, U.S. Serial No. 13/382380, with claims 1-7 and 22 directed to a method for surface decontamination of a pre-filled container.

5. I understand that the PTO Patent Examiner has rejected claims 1, 4, 5, 7, and 22 as obvious over Metzner *et al.*, published U.S. Patent Application No. 2003/0003014 ("Metzner"), as evidenced by and in view of Hasegawa et al., U.S. Patent No. 6,228,324 ("Hasegawa") and further in view of Dalmasso et al., U.S. Patent No. 5,788,941 ("Dalmasso"). I have read and understand Metzner, Hasegawa and Dalmasso. The Examiner asserts that Metzner teaches the claimed method, but that the "method taught by Metzner includes a step of lowering the pressure in the treatment chamber below ambient atmospheric pressure prior to the application of hydrogen peroxide and subsequent decontamination." (January 3, 2013 Office Action, page 5). In response to the Applicants' assertion that the claimed method does not include the step of lowering the pressure prior to application of H_2O_2, the Examiner cited Dalmasso for its teaching that "effective sterilization can be achieved at atmospheric (ambient) pressure and room temperature." (*Id.*). The Examiner concludes that a "person having ordinary skill in the art at the time of the invention would have found it obvious to simplify the method taught by Metzner by applying the hydrogen peroxide vapor causing subsequent decontamination at ambient (atmospheric) pressure … with a reasonable expectation of success as taught by Dalmasso et al." (*Id.*).

6. I believe that the Examiner's conclusion with regard to Metzner is incorrect. The method taught by Metzner would likely result in denaturation of the protein in the syringe, or a non-sterile pre-filled syringe, or both. More specifically, if the method of Metzner were used, i.e., carrying out the sterilization under vacuum, this would likely cause a breach in the syringe seal, which in turn could cause entry of the H_2O_2 into the syringe. This would cause denaturation of the protein in the syringe, which is sensitive to H_2O_2-facilitated degradation. In addition, in the vacuum method taught by Metzner, if the syringe in question contained an air bubble (even a very small air bubble), the plunger stopper in the syringe would be pulled back by a certain distance upon application of the vacuum, and would thus cover parts of the inside of the syringe barrel, preventing these parts from exposure to the H_2O_2 and thus from sterilization. And, subsequent to the sterilization step, when the vacuum is released, the plunger would move back into its original position and expose this non-sterile surface to the environment. Thus the vacuum method taught by Metzner may not result in a sterile product. Metzner does not teach any steps that can be taken to avoid breach of the syringe seal or movement of the syringe as the vacuum is applied and then removed. One possible solution to

these problems resulting from using the method of Metzner would be to use a method such as the claimed method, in which there is no pressure change during the sterilization process.

7. The Examiner contends that one such method is that taught by Dalmasso. I believe that the Examiner's conclusion with respect to Dalmasso is incorrect, for the reasons stated below. As a first matter, I would not look to the teachings of Dalmasso for guidance if I were seeking a method of sterilizing a primary container, e.g., a syringe, containing a protein sensitive to H_2O_2-facilitated degradation, wherein the syringe was itself packaged in a secondary container prior to sterilizing. And, even if I was already aware of the teachings of Dalmasso, I do not believe that the teachings of Dalmosso, taken alone or combined with those of Metzner (or any of the other references cited by the Examiner in this case), could help a person of ordinary skill in the art to arrive at the claimed invention with any expectation of success. The method taught by Dalmasso relates to a completely different technical problem than the one addressed by the claimed invention, i.e., sterilization of bone tissue prior to transplantation. Dalmasso states that the bone tissue can even be pre-treated with liquid hydrogen peroxide solution, which gives evidence that bone tissue is not sensitive to H_2O_2 (column 4, line 42), unlike the protein in the syringe in the claimed invention. In addition, the method taught by Dalmasso does not use secondary packaging for the bone tissue to be sterilized. In fact, Dalmasso teaches that if penetration of the bone beyond its cortical surface is needed, sterilization under vacuum may be desired, and even then, fat and marrow that fill spaces within the bone should be removed to allow the H_2O_2 vapors to enter these spaces. (See Dalmasso at column 4, lines 3-5). Thus, Dalmasso indicates that in the absence of a vacuum, only limited penetration into the surface of the bone is achieved, and even then, that is when there is no packaging around the bone. In short, contrary to what the Examiner contends, it is not a simple, trivial matter to merely perform the Metzner method at ambient (atmospheric) pressure based upon the teachings of Dalmasso. Put another way, the Metzner and Dalmasso methods could not be combined with any expectation of success.

8. A person of ordinary skill in the art when seeking a method of sterilizing a syringe, containing a protein, wherein the syringe is itself packaged in a secondary container, would not look to the Dalmasso reference for guidance, and certainly would not look to combine non-analogous methods, i.e., Metzner and Dalmasso, with any expectation of success.

9. With the claimed invention, the syringe, the surface of which is to be sterilized, is sealed in secondary packaging. Conventional thinking, at the time of filing the current patent application, was that in order to get the sterilizing agent to penetrate the packaging, a vacuum would have to be applied. However, as I state above, that carries with it the risk that (i) the seal of the syringe is compromised, leading to degradation of the protein product, or (ii) that the plunger is moved during application and removal of the vacuum, leading to incomplete sterilization. The present application disclosed for the first time, and contrary to conventional thinking, that it is possible to obtain sufficient sterilization of the outer surface of a syringe in secondary packaging at ambient pressure.

All statements made herein based on knowledge are true and all statements made herein based on knowledge and belief are believed to be true. All statements made herein were made with the knowledge that willful false statements and the like may jeopardize the patentability of the above patent application and the validity of any patent that issues from it, and may subject me to penalties, including fines and imprisonment, under Section 1001, Title 18 of the United States Code.

Respectfully submitted,

Date: 24 May 2013

Juergen Sigg, Ph.D.