Exhibit 1014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	KOTTAYIL, S. George, et al.	Confirmation No.:	4756
Serial No.:	11/698,739	Group Art Unit:	1646
Filed:	January *25,* 2007	Examiner:	Sandra WEGERT

FOR: SUBLINGUAL FENTANYL SPRAY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT/RESPONSE

In response to the Office Action dated June 8, 2012, please amend the above-identified patent application in the following manner:

Amendments to the Claims are reflected on the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Amendments to the Claims:

Set forth below in ascending order, with status identifiers, is a complete listing of all claims currently under examination. Changes to any amended claims are indicated by strikethrough and underlining. This listing also reflects any cancellation and/or addition of claims.

Claims 1-143. (Cancelled).

144. (Currently Amended) A unit dose of a non-propellant sublingual fentanyl formulation comprising discrete liquid droplets of an effective amount of fentanyl and a pharmaceutically acceptable liquid carrier, wherein the sublingual fentanyl formulation comprises:

from about 0.1% to about 0.8% by weight of fentanyl or a pharmaceutically

acceptable salt thereof;

from about 20% to about 60% by weight of ethanol; and
from about 4% to about 6% by weight of propylene glycol;

~~wherein said discrete liquid droplets have a size distribution of from about 5 µm to about 500 µm, and a mean diameter of about 20 µm to about 200 µm;~~

wherein after sublingual administration to a human, said sublingual fentanyl formulation provides[~~:~~]

~~a mean maximum plasma concentration (C_{max}) of fentanyl of from about 158 pg/mL to about 177 pg/mL per 100 µg fentanyl;~~

a mean time to maximum plasma concentration (T_{max}) of fentanyl of from about 10 to about 60 minutes~~; and~~

~~a mean area under the plasma concentration time curve to infinity (AUC_∞) of fentanyl of from about 715 pg•hour/mL to about 1061 pg•hour/mL per 100 µg fentanyl~~.

145. (Previously Presented) The unit dose of claim 144, wherein said discrete liquid droplets have a size distribution of from about 10µm to about 200 µm.

146. (Cancelled).

147. (Cancelled)

148. (New) The unit dose of claim 144 wherein after sublingual administration to a human, the sublingual fentanyl formulation provides a mean time to masimum plasma concentration (Tmax) of fentanyl from about 5 to 120 minutes.

REMARKS/ARGUMENTS

I. Status of the Claims

Claims 144-145 are pending. Claim 144 has been amended and claim 148 has been added to reflect "time-to-onset-of-action" in terms of the formulation and Tmax as supported by the Application (pages 3 and 5 and the original claims) and by the Declaration of Dr. Larry Dillaha submitted herewith. No new matter has been added.

II. The Claims

The pending claims recite various "compositional" limitations (i.e., amounts of fentanyl, ethanol, propylene glycol), and pharmacokinetic (PK) limitations. These claims recite a unique formulation which has unique characteristics and efficacy as mentioned herein.

As evidented by the Declaration of Dr. Larry Dillaha submitted herewith, the clinical efficacy has clear advantages which are neither predictable or expected. In particular, when compared to placebo and all commercial transmucosal immediate release fentanyl formulations, the claimed unit dose provides statistically significant relief as early as 5 minutes whereas the competitive products do not begin relief until at least 10-15 minutes for breakthrough pain in cancer patients. This is significant and critical.

The cited reference US 2006/0062812 (Ross) is inferior with respect to the composition of the formulation of the present unit dose and does not disclose, suggest or recognize the importance of the composition. Furthermore, *Ross* fails to disclose clinical efficacy better than a 30 minute onset. Accordingly, the compositional differences and such unexpected results render the present claims non-obvious. As a result, the present claims are patentable over *Ross*.

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