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Our Ref: 393 CS-AU

Subject: Response to Examination Report
Patent Application no. 20165202751 (Malter)

We refer to the examination report.

The applicant requests amendment of the application in accordance with the Statement of Proposed Amendments below.

In answer to objection 1, Claims 1 and 7 have been amended to distinguish the present invention. Claim 7 now defines:

7. A method of non-invasive treatment of both surface and deep body bacterial and viral infections via microorganism corresponding discrete low intensity direct electric currents (LIDCs) that pass through the high electrical resistance of intact skin for deep infections, the method comprising

providing a control unit with a real-time microcontroller regulated nanoampere output current resolution and accuracy in the ultra-low LIDC range further calibrated by self-adaptive algorithms and full-feedback proportional-integral-derivative control,

providing a pair of cutaneous electrodes connected to the control unit having extremely high, intact skin interfacing electrical conductivity,

positioning the electrodes on anatomically opposite planar surfaces superficial to the aligned deep body infection target,

performing surface wound healing treatment by creation of an electric field in polarity, strength and topography matched to the individual endogenous wound-generated

electric field, derived from direct bioelectric measurement by the control unit and self-adaptively via series resistor algorithmic software wound modeling with resistor voltage drops corresponding to endogenous bioelectric properties of the various types of tissues aligned between the electrode pair.

Claim 1 is similarly worded and defines corresponding features.

Basis for the amendments is from the specification and drawings as filed, as highlighted in the attached document – Complete Description - Basis for Amendments. Amended claim 7 is on page 29 of this document with support for the terms in the claim highlighted in the specification with the corresponding colour highlight.

Claims 1 and 7 are distinguished from the cited references as follows:

1. BACKGROUND TO STANDARD "IONTOPHORESIS" AND COMPARISON WITH D1 AND D2

Prior to the present invention, "iontophoresis", also called, "transdermal drug delivery", as described in D1 and D2, is known and applied as a method of delivering and transporting a pharmaceutical drug (the "active principle") held against the skin in liquid form ("ionic form") [D1 column 1 line 18-19, column 4 line 65-66] within an absorbent material or 'reservoir' being part of the 'active' electrode (pad), transdermally (i.e., across the skin), with the aim of, and actually, penetration of approximately 5-10 millimeters[1,2] into the body, resulting in the delivered drug reaching and being absorbed by superficial capillaries in the skin, these leading to the connecting venules and arterioles, and so then gradually the drug being transported into larger blood vessels, until it eventually enters the systemic circulatory system of the body.

Typical electric currents used are always in the milliampere (mA) range, compared to microampere currents ('low intensity direct current' (LIDC) and ultra-low LIDC as disclosed in the present invention). The overall and specific aim of "iontophoresis" is not to target isolated treatment to and of a specific body part for remedying the pathology of that body part, but simply to deliver the drug into the general bloodstream. The exception is cortisol "iontophoresis" into superficial inflamed surface tissues such as occur in localized soft tissue trauma injury, which are the direct targets of these "iontophoresis" treatments, but even in these applications of "iontophoresis", the penetration of the pharmaceutical drug (therapeutic agent) is known to remain very superficial to a depth of only a few millimeters.

Confirming the above background explanation, as a general example of “iontophoresis”, please note that D1 describes the standard "iontophoresis" electrode configuration of "two adjacent electrodes applied to the skin of the patient." [column 1 line 21-22], that is, the two electrodes are placed a (usually relatively small) distance apart on the same anatomical surface of the body (part). This standard, generally applied “iontophoresis” electrode positioning demonstrates that there is no intention nor claim nor actual possible technical means of targeted treatment of an internal body part, because in this standard "iontophoresis" electrode configuration, the electric current will (due to basic Physics principles) take the path of least electrical resistance, and travel in a straight line pathway between the two adjacent electrodes—never entering the body to any depth beyond a few millimeters—in fact passing between the top layer of skin the stratum corneum consisting of dead skin cells and having relatively high electrical resistance, and the most electrically conductive and superficial dermal layers of the skin immediately below the stratum corneum.

All of these arrangements and mechanisms of action of standard "iontophoresis" as mentioned in D1 and D2 are well known, established and reported in the prior medical scientific literature.

Briefly, D1 discloses "A method for measuring the cutaneous electrical resistance of a patient undergoing transdermal administration of medication assisted by an iontophoresis current,", and D2 discloses [0013] “devices and methods for administering a drug through a body Surface (e.g., skin)”, both of which are standard “iontophoresis” methods and devices.

D2 prefers the term "electrotransport” but is essentially identical to D1, in so far as being standard “iontophoresis". A “load current in operation [] designed to be a predetermined value Io. typically on the order of 1 mA.” is a typical range value for “iontophoresis", as noted above, and is not LIDC.

More specifically, D1 and D2 do not disclose

positioning the electrodes on anatomically opposite planar surfaces superficial to the aligned deep body infection target,

performing surface wound healing treatment by creation of an electric field in polarity, strength and topography to the individual endogenous wound-generated electric field, derived from direct bioelectric measurement by the control unit and self-adaptively via series resistor algorithmic software wound modelling with resistor voltage drops corresponding to endogenous bioelectric properties of the various types of tissues aligned between the electrode pair

which must be done in order to deliver a therapeutic low intensity constant-current—being the therapeutic agent itself rather than a pharmaceutical drug—to that internal body part, such as an internal organ or other localized anatomical structure such as, for example, the aortic arch of the thoracic aorta.

Theoretically, even if the electrode pairs mentioned in the specifications of either D1 or D2, or in any other standard “iontophoresis” application of which D1 and D2 are examples thereof, were positioned such as to anatomically cross-section an anatomical internal body target having a viral or bacterial infection, with the conscious and specific aim of treating that infected body part, the pharmaceutical drug contained in the drug-delivery electrode cannot possibly penetrate to the required internal body depth, as explained above, and so such infection treatments with standard “iontophoresis” applications cannot be achieved, being absolutely technically impossible.

Specifically again, neither D1 and D2 disclose a system and low intensity direct current (LIDC) medical iontophoresis method for targeted (i.e. focused) treatment of an internal body part having a bacterial or viral infection, using an ultra-low constant-current as a therapeutic agent, rather than a pharmaceutical drug.

The present invention is not self-evident, nor obvious from D1 nor D2, nor from any other standard "iontophoresis" practices that do not aim to nor actually can achieve the treatment of an internal (i.e., anatomically deep) body part having a localized infection, and is also not general knowledge. The devices and methods of D1 and D2 are technically incapable of carrying out these treatments, regardless of persons skilled in the art of "iontophoresis", and cannot possibly be arrived at via routine trial and error using the equipment described in D1 or D2 nor of a variation thereof: An aqueous ionic medication as discussed in D1 and D2 regardless of any extra drug delivery safety innovations, cannot penetrate beyond approximately 10 millimeters into the body and cannot provide a targeted, isolated treatment of an internal body part having an infection.

[1] https://academic.oup.com/ptj/article/83/2/161/2857547

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3419556/

DIFFERENTIATING FEATURES IN MORE DETAIL

2. ELECTRODE CONFIGURATION

In complete contrast to D1, the present invention discloses, in some of its parts, as follows [please note corresponding asterisked phrases in (15) and (42)]:

(15) The present invention also provides a *method of low intensity direct current and medical iontophoresis for treatment of a body part*, the method comprising:

placing at least one pair of *electrode pads on opposing margins or sections of the body part*,

operating a control unit to create a resistance measuring circuit, a current producing circuit, and/or a voltage producing circuit with the electrode pads across the body part.

&

(42) Briefly, in use, the electrode pads 32 are placed in contact with the patient's body *to anatomically cross-section a target anatomical area or location, often an organ, bone, etc*. In another example, the electrode pads 32 are *placed adjacent to the wound edge and behind the wound on the anatomically opposite surface of the injured body part*.

In explanation of sections (15) & (42) of the present application, first, in the present invention, as stated, the ultra low amperage electric constant-current (LIDC) itself is the therapeutic agent (medicine); there is no pharmaceutical drug iontophoretically introduced into the body. The novel electrode configuration of the present invention anatomically cross-sections the target tissue, so that the therapeutic LIDC (due to basic Physics principles) taking the pathway of least electrical resistance, will travel in a straight line pathway between the two electrodes, and so will pass directly through the target (infected) tissue(s) aligned between them. For example, if the two electrodes (pads), of dimensions 10cm x 15cm in one embodiment, are placed on opposing flanks of the body at the height of the liver, and angled slightly so as to match the longitudinal anatomical planar shape of the liver, the electric constant-current will pass from (+)positive to (-)negative electrodes directly through the liver and from one side to the other of the entire body via deep internal body pathways.

This cross-sectioning electrode configuration is not obvious nor a variation from standard "iontophoresis" applications, since with standard "iontophoresis" methods there is no possible advantage of positioning the 'return' (-ve) electrode on the opposite anatomical surface of the body part onto which the active (+ve) electrode is placed, for the reasons outlined in section 1, and is consequently not reported in the associated literature:

http://www.electrotherapy.org/modality/iontophoresis#Basic%20Principles

3. DISCRETE LOW INTENSITY DIRECT CURRENTS (LIDC) FOR INFECTION TREATMENTS AND METHODS OF TRANSPORTATION ACROSS THE SKIN BARRIER

Additionally as part of the treatment system of the present invention, (69) discloses two discovered, specifically discrete, ultra-low LIDCs that are applied, with the aims and effects of the flow of these LIDCs, through the skin layers and deep into the body, with the ability to attenuate or inactivate either a bacterial or viral infection.

D1 also refers to low intensity direct currents (LIDC) as also mentioned in the present invention, for example in D1 in the linear section of Fig.:1 in the section 0A (solid and dotted lines), labeled "0-200uA". However, these are disclosed in D1 as the measuring currents only, delivered prior to the actual standard iontophoresis treatment, these measuring currents and voltages being generated in order to gain a linear plot of values of relationships between voltages and currents for the individual patient's skin, which is the stated purpose, scope and function of D1, not for treatment purposes. In comparison, it is general knowledge as noted above, that "iontophoresis" of a medication in ionic liquid form (the treatment itself) can only be achieved with higher, milliAmpere ("mA") electric currents, which is also stated in D1 [column 4 line 19-20] and in D2 [0050] as “typically on the order of 1 mA.”.

These facts further demonstrate the novelty of the present invention, where ultra-low constant LIDC (being discretely 2.5 microamperes (uA) and 7.5uA, for bacterial and viral infection treatment, respectively), and being of the order of a thousand times smaller electric currents (uA vs mA) than standard “iontophoresis”, are themselves the therapeutic agents (medicine); and which additionally—differentiating the present invention from D1 & D2—can penetrate through the skin layers of the body then deep into the body without needing to follow an anatomical structure nor physiological pathway nor rely on the vascular system as with standard “iontophoresis”, in order to affect a bacterial or viral infection treatment of a targeted, isolated infected body part, including for example a targeted internal organ of the body.

It is also important to note that the discrete LIDCs disclosed in the present invention, are not simply two ultra-low LIDC values selected to have an arbitrary difference in their magnitudes from smaller to greater, with a relatively small difference of intensity value between them. Instead, the therapeutic effects of the two disclosed currents, 2.5 microamperes (uA) and

7.5uA, have specific 'affinities' to a bacterial infection treatment and to a viral infection treatment, respectively.

Furthermore, these LIDCs are 'discrete', meaning that the therapeutic effects of slightly lower and higher LIDCs than these two precisely selected LIDCs, reduce very significantly when either of these two LIDCs are increased or decreased, such that if therapeutic effects from application of either of these two LIDCs were plotted graphically, effect plotted quantitatively on the vertical (y) axis and current intensity along the horizontal (x) axis, they would describe bell curves with sides having steep linear aggregate gradients down to zero on the y axis, with only approximately 1uA total distributions along the x axis for both 2.5uA and 7.5uA, beyond which therapeutic effects for bacterial and viral infection treatments, respectively, are very significantly less and often essentially nil. That is, at 1.5uA and 3.5uA, and at 6.5uA and 8.5uA, there are virtually no therapeutic effects for these specific medical intervention intentions for infection treatments. These bell curve specificities of exactly these two LIDCs are another feature of the present invention, which is not obvious from the previously published literature. Though the complete mechanisms of actions of these LIDCs are not fully known—as with many established medical treatments, their empirical (i.e., symptomatic) and laboratory pathology evidence, clinical therapeutic effects and 'bell curve' limitations, are confirmed.

This discovery, disclosed in the present invention of specific effects of highly discrete LIDCs may have some relationship in terms of mechanisms of action to much earlier research, as shown in FIGURE 6 in the following work:

https://siselectromed.com/wp-content/uploads/2017/02/Becker_et_al-1967-Transactions_of_the_New_York_Academy_of_Sciences.pdf

This work is cited to give further validity and explanation towards understanding the fuller mechanisms of action of the present discovery and invention of these highly discrete LIDCs, applied non-invasively, having bacterial and viral infection treatment effects; though this cited work does not claim nor disclose LIDCs for infection treatments.

Though the present invention does not need to be bound by theory, it must be assumed that the specific, discrete ultra-low constant LIDCs disclosed in the present invention and mentioned above, in turn generated by very low voltages, are included in the narrow range of those unusually capable of crossing the skin barrier where "at relatively low voltages (U < 30 V) this [the] drop of skin resistance can be attributed to electroporation of the appendageal ducts" that run through the stratum corneum: https://www.ncbi.nlm.nih.gov/pubmed/9533696

This is very important to note, because the skin normally has an electrical resistance of at least 50 kiloOhm and up to 1 megaOhm when very dry mostly contributed by the stratum corneum, when interfaced with cutaneous electrodes; and it is generally known that such small ultra-low

constant LIDCs and voltages cannot usually cross the skin barrier (skin layers) given its high, total electrical resistance. Whereas, in contrast, high frequency waveform currents and voltages, can, and much higher direct currents (DC) and voltages, also can. Thus, some way must be found to overcome the high electrical resistance of the skin if a treatment of an internal body part is to be achieved using a low and even very low intensity direct constant-current. However our confirmed therapeutic effects for internal body infection treatments using ultra-low LIDC, force the conclusion that the specific ultra-low constant LIDCs disclosed in the present invention, lie within this physiological range where electroporation of the appendageal (sweat) ducts occurs, and do penetrate deep into the body, and so must, at least in part, be crossing the skin barrier's high electrical resistance with the "electroporation of the appendageal ducts" being the transdermal 'transport' mechanism of action. This novel *in vivo* finding is further evidenced and confirmed, when the equipment disclosed in the present invention is applied to the body, using standard digital multimeter performed, reproducible, equating, standard electronics series circuit measurements of current-in vs current-out (both DC) between the pair of applied SIS electrodes cross-sectioning a body part or the whole body from side to side in the example of a treatment of a liver organ as mentioned above, demonstrating this fact of LIDC flow between electrodes through the body as disclosed in the present invention.

Lastly, in some disclosures in the prior art, LIDC is used to treat an internal body part, such as a bone, but only via an invasive, temporary or permanent implanted electrode. The present invention is non-invasive, with both electrodes applied to the skin, and does not rely on an active implanted electrode.

There is prior, patented documentation for direct current and LIDC treatment of surface infections, surface wounds, for example:

Therapeutic low intensity direct current generator with polarity reversal

"This invention relates generally to low intensity direct current treatment of skin ulcers and the like."

https://patents.google.com/patent/CA1069183A/en?q=direct&q=current&q=infection&oq=direct+current+infection

Method for treating herpes simplex

"an apparatus and method for treating infectious skin conditions"

https://patents.google.com/patent/US5133352A/en?q=direct+current&q=infection

To achieve infection treatment effects for surface infections, the electrode pair is placed on the same anatomical surface of the body part, a small distance apart, as also per standard pharmaceutical drug “iontophoresis” as described in D1 & D2.

However, these are all treatments for surface skin infections only, and do not disclose any methods nor system nor devices for effective treatment of an internal body part having a viral or bacterial infection where a LIDC must cross intact skin, which has not been done before the present invention.

3.5. GENERATION OF HIGH PRECISION ULTRA-LOW LIDCS

Based on the requirements for effectiveness described in section 3 in relation to LIDCs, the present invention additionally specifies that the generation of these LIDCs:

(29) [] have a high degree of accuracy of [] current and voltage production of these parameters (resolution/accuracy: ±100 nanoamperes, []), that are further calibrated for increased accuracy beyond these values by internal algorithms and an on-board full-feedback proportional-integral-derivative (PID) controller that corrects for deviations across wide output and measurement ranges, as well as environmental operating parameters such as temperature, humidity, etc, not available in the prior art.

With this extreme constant-current generation and maintenance precision, the therapeutic effects of the discrete LIDCs mentioned in section 3, are possible. None of the electronic circuitry designs of D1, D2 & D3 are capable of these precisions, as these requirements were evidently not part of their design specifications; whereas such high accuracy and resolution output current generation requires unique constant-current source electronics circuits design/engineering and componentry, which are also features on the present invention.

4. ELECTRODES AND ELECTRODE APPLICATION

As outlined above, only at specific low voltages and currents can a LIDC cross the skin layers. In order to achieve this effect, a cutaneous electrode is required having lower electrical resistance properties than standard electrotherapy electrodes of various kinds, which typically contribute ≥400 kiloOhms resistance per pair connected in series with the body (part) inbetween completing the circuit.

The SIS electrode disclosed in the present invention has been designed to achieve, when wet and applied to intact skin, ≤20 kiloOhms, and often achieves ≤5 kiloOhms per pair. Their greatly superior conductivity allows the discrete LIDCs for infection treatments to be generated at very low voltages, and thereby cross the skin barrier by the means explained above. Normally, such LIDCs generated at low voltages—millivolts, will not cross the skin barrier. Standard "iontophoresis" electrodes, of any variation, also cannot be used do their much higher contributing electrical resistances, which would then require much higher voltages that would create skin damage and so not facilitate flow of current to inside the body.

Though the use of silver-nylon as a wound "dressing" has been used before[3] for wound infection treatments, it has not been used on intact skin as a cutaneous electrode as part of a non-invasive method and system of treatment of a localized internal body infection via the mechanisms of action described above in sections 2-3.5, and its use in this way is not obvious from its prior applications only onto exposed, damaged tissues.

5. INTEGRATION OF MULTIPLE ELEMENTS INTO A TREATMENT SYSTEM WITH MULTIPLE NARROW OPERATING LIMITS

For the method and non-invasive treatment system disclosed in the present invention to be effective, integration of the application of the specially constructed SIS electrodes and the electrode configuration cross-sectioning a target internal body infected location, and the discrete LIDCs discovered to have specific correspondences to whole classes and families of either bacterial or viral species, generated and maintained with extremely high precision (≤±100 nanoamperes) at low voltages so that they can cross the skin barrier by the mechanisms of action described in sections 3-4, are integrated together within very narrow operating limits for these target and actual therapeutic effects to be achieved, none of which is obvious nor has precedent as being reported before in the medical-scientific literature nor in a research setting of such treatments for human or non-human animals. This complex integration of the components, functional elements and methods of the entire treatment system disclosed in the present application, forms another part of the present invention.

[3] https://siselectromed.com/research/#silver-nylon

6. WOUND HEALING APPLICATION

We now further refer to the following sections of my the present application:

(46) Medical iontophoresis system – WOUND operational mode

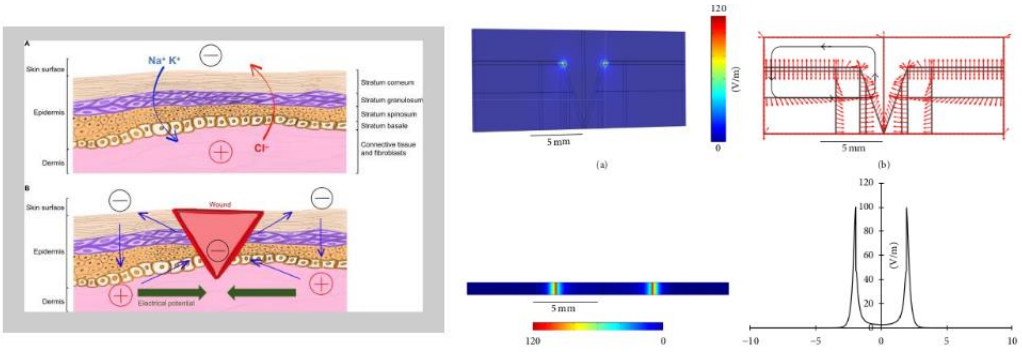
(47) Figure 3 shows a first mode of operation for treatment of acute or chronic surface wounds, deeper wounds, ulcers, abscesses, other lesions, osteomyelitis, and surgical site infections and protection

& (50), (51), (52), (56) & (57).

The present invention also provides an actual treatment system for wound healing, comprising several electrical stimulations. Though one of these electrical stimulations is similar to surface infection treatments with LIDC, there are additional, complete and novel differences included in the other electrical stimulations only disclosed in the present application.

(50) Discloses a method of applying electrodes to a surface wound that allows creation of an electric field (EF) from the voltage producing circuit of the device, which is biomatching to polarity, topography and field strength of the endogenous wound-generated EF (WGEF), which is established in the medical-scientific literature to be important for wound healing and closing, as first mentioned in (56) and then described in more detail in (57)d).

The following diagrams are extracts from the medical-scientific literature, describing the phenomenon of the WGEF; though they do not include any information on how to reproduce the WGEF via electrical stimulation nor biomedical engineering to result in dynamically, biomatching WGEF parameters that can be used for electrical stimulation as mentioned here and disclosed in (50) of the present invention.



To produce this result, according to the present invention, the electrodes are positioned on anatomically opposite surfaces of the injured body part (the surface wound); which also minimizes the chance, during the infection treatment electrical stimulation stage (57)c) that silver cation flow from the (+)positive electrode will pass through the skin between the two electrodes—instead of penetrating deeper into the wound bed—as it certainly would (due to basic Physics principles) if the electrodes were arranged as mentioned in D1 or D2.

Additionally, (57)d) discloses a method of computing the WGEF value for the individual wound from the through-wound resistance measurement value obtained at any stage as the wound heals, via the resistance measuring circuitry of the device:

The process indirectly measures the wound-generated electric field in real-time by skin resistance measurements and known values of the TEP [transepithelial membrane potential] and of the relative voltage potentials at the wound margins, and supplements the wound-generated electric field in a real-time scaled manner to the wound properties so as to generate a bioelectrically matching magnitude and polarity voltage drop at the wound edges.

(51) & (52) describe variant embodiments of electrode positioning to the wound depending on various real-world factors that might be encountered.

The realtime method of self-adaptive scaling of the artificially introduced WGEF (electrical stimulation), as shown in FIGURE 3a and outlined in (57)d), is a feature element of the wound healing treatment system disclosed by the present invention.

These WGEF replacement/supplementation results and subsequent wound healing effects are not obvious from the specifications and disclosures in D1 nor D2, nor from trial and error via any of their elements nor applications, and have never been performed before using standard “iontophoresis” methods and devices, about which D1 & D2 serve as examples thereof.

7. DIFFERENTIATING FEATURES FROM D3

Many of the differentiating features of the present invention mentioned above, also apply in respect of D3. D3 refers to [0003] “the electrical treatment of malignant tumors and neoplasms by applying a Voltage to affected tissue”, and [0010] “relates generally to a method of treating cancer. It involves a device, either partially or totally implanted, consisting of a generator and one or more wires (or leads) containing one or more electrodes. The electrodes are implanted in or near the tumor and the generator may be implanted subcutaneously as close to the tumor as practical.

The present invention discloses a completely non-invasive method and treatment system. D3 is an invasive electrical and “iontophoresis” treatment system for a neoplastic growth (commonly called “cancer” or “malignancy”). D3 depends on the implanted electrode(s) being inserted such that they are brought in close proximity to the neoplasm or even making contact with it, with relatively high voltages [for example, 5-10Volts, Fig. 27B] then applied to destroy the neoplastic cells, and an implanted device that releases a cytotoxic chemotherapy agent towards or into the neoplasm.

Using the same explanations given above in relation to D1 & D2, the methods and devices disclosed in D3 are not possibly, technically capable of carrying out, non-invasive internal body localized infection treatments with LIDCs, regardless of persons skilled in the art of "iontophoresis", and cannot possibly be arrived at via routine trial and error using the equipment described in D3. As such examples, D3 does not disclose electronic methods of generation and application to the body surface of LIDCs that can overcome and cross the skin barrier at low applied voltages and affect internal body infection treatments, which are all features of the present invention.

8. OTHER ELECTRONIC CIRCUITRY SIMILARITIES COMPARED

The mention of current producing, voltage producing and resistance measuring circuits in D1 [column 5 line 36-55], D2 and D3 are thus only partial similarities to the present invention and only in terms of electronic circuits also included in these inventions. The meaning here is analogous to a domestic bread toaster and kitchen refrigerator both having current producing circuits, but that these circuits only comprise a partial, non-defining, non-total descriptive componentry part similarity between the two devices, where one device (toaster) does not make the other (refrigerator) obvious nor derivative from the other in any way whatsoever.

We also request withdrawal of the postponement of acceptance.

Favourable reconsideration is requested.

Yours Sincerely,

Fidel Dela Paz

Statement of Proposed Amendments

1. Replace all description and claims pages on file with new description and claims pages lodged herewith in duplicate.