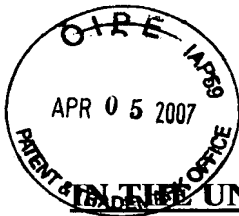


## Exhibit 1004

‘183 Patent File History (“FH183”)  
Amendment 4/5/2007



**UNITED STATES PATENT AND TRADEMARK OFFICE**

In re patent application of:

Plachetka, *et al.*

Appl. No.: 10/741,592

Filed: December 22, 2003

For: **Multilayer Dosage Forms Containing  
NSAIDs and Triptans**

Art Unit: 1615

Examiner: Sharon Kennedy

Atty. Dkt.: 7569/80923

**Amendment and Response Under 37 C.F.R. §1.111**

Commissioner of Patents  
U.S. Patent and Trademark Office  
Customer Service Window, MS Amendment  
Randolph Building  
401 Dulany Street  
Alexandria, VA 22314

Sir:

In response to the Office Action dated December 20, 2006, Applicants respectfully request reconsideration of the above-captioned application in view of the following amendments and remarks.

**A Listing of Claims** begins on page 2 of the present document.

**Remarks/Arguments** begin on page 5 of the present document.

**Amendments to the Claims**

Please amend claims as shown below in the List of Claims.

**List of Claims**

1. (Currently) A multilayer pharmaceutical tablet comprising naproxen and a triptan and, wherein:
  - a) substantially all of said triptan is in a first layer of said tablet and substantially all of said naproxen is in a second, separate layer; and
  - b) said first layer and said second layer are in a side by side arrangement such that the dissolution of said ~~NSAID~~ naproxen occurs independently of said triptan.
2. (Original) The tablet of claim 1, wherein said naproxen is in the form of naproxen sodium at between 200 and 600 mg.
3. (Original) The tablet of claim 1, wherein said triptan is selected from the group consisting of: sumatriptan, eletriptan, rizatriptan, frovatriptan, almotriptan, zolmitriptan, and naratriptan.
4. (Original) The tablet of claim 1, wherein said triptan is sumatriptan.
5. (Original) The tablet of claim 4, wherein said sumatriptan is in the form of sumatriptan succinate at between 25 and 100 mg.
6. (Original) The tablet of claim 1, wherein said first layer and said second layer are juxtaposed symmetrically along a single planar surface such that essentially all of said first layer is on one side of said planar surface and essentially all of said second layer is on the other side of said planar surface.

7. (Original) The tablet of claim 6, wherein said first layer and said second layer contact one another along said single planar surface.
8. (Original) The tablet of claim 6, wherein said first layer and said second layer are separated by at least one additional layer.
9. (Original) The tablet of any one of claims 1-8, wherein said tablet is a bilayer dosage form.
10. (Original) The tablet of any one of claims 1-8, further comprising a coating layer surrounding both said first layer and said second layer.
11. (Original) The tablet of any one of claims 2, 3 or 6-8, wherein said triptan is sumatriptan.
12. (Original) The tablet of claim 11, wherein said sumatriptan is in the form of sumatriptan succinate at between 25 and 100 mg.
13. (Original) A method of treating a patient for headache, comprising administering to said patient the tablet of any one of claims 1-8, wherein said patient is treated at a dosage effective to alleviate the pain associated with said headache.
14. (Original) The method of claim 13, wherein said headache is migraine headache.
15. (Original) A method of treating a patient for headache, comprising administering to said patient the tablet of claim 9, wherein said patient is treated at a dosage effective to alleviate the pain associated with said headache.
16. (Original) The method of claim 15, wherein said headache is migraine headache.

17. (Original) A method of treating a patient for headache, comprising administering to said patient the tablet of claim 10, wherein said patient is treated at a dosage effective to alleviate the pain associated with said headache.
18. (Original) The method of claim 17, wherein said headache is migraine headache.
19. (Previously presented) A multilayer pharmaceutical tablet comprising an NSAID and a triptan, wherein
  - a) substantially all of said triptan is in a first layer of said tablet and substantially all of said NSAID is in a second, separate layer; and
  - b) said first layer and said second layer are in a side by side arrangement such that the dissolution of said NSAID occurs independently of said triptan.
20. (Previously presented) A method for rapid release of sumatriptan and naproxen from an oral dosage form in a patient, the method comprising administering to said patient the tablet of claim 4 or claim 5, wherein in said patient, dissolution of sumatriptan and naproxen is faster from said tablet as compared to dissolution of sumatriptan and naproxen from a tablet where sumatriptan and naproxen are in a physical admixture.

## **Remarks**

### **I. Status of the Application and Claims**

As originally filed, the present application had a total of 18 claims. Claims 19 and 20 were added in a Preliminary Amendment filed by Applicants on August 30, 2005. No further addition or cancellation of claims has taken place herein.

### **II. The Amendments**

Claim 1 was amended to correct a minor error pointed out by the Examiner. Specifically the term "NSAID" in paragraph b) was changed to "naproxen." This amendment does not add new matter to the application and its entry is therefore respectfully requested.

## **The Rejections**

### **I. Rejection of Claims Under 35 USC § 112, Second Paragraph**

On page 2 of the Office Action, the Examiner rejects claims 1-20 under 35 USC §112, second paragraph. It is alleged that the claim is indefinite because there is insufficient antecedent basis for the phrase "said NSAID" in paragraph b) of claim 1.

In response, Applicants have amended paragraph b) in claim 1 so that it now refers to "said naproxen" rather than "said NSAID." In light of this amendment, Applicants respectfully submit that the Examiner's rejection has been overcome.

### **II. Rejection of Claims Under 35 USC § 103**

On pages 2 and 3 of the Office Action, the Examiner rejects claims 1-20 under 35 USC §103 as being unpatentable over Plachetka (US 5,872,145) in view of Swintosky (US 2,951,792). The Plachetka reference is cited as disclosing dosage forms containing naproxen and triptans and the reference by Swintosky is cited as demonstrating that the concept of separating tablet ingredients into different layers has long been known.

Applicants respectfully traverse this rejection.

Applicants do not dispute the Examiner's allegations that drug combinations utilizing triptans and naproxen were known in the prior art or that the concept of putting drugs in separate layers of dosage forms was well established. However, Applicants submit that the claims are directed to patentable "selection invention." In order to better understand the exact meaning of the terms that are used in the claims, reference should be made to the specification, and in particular, to page 3, lines 15-26, which read as follows:

The layers [of the claimed dosage forms] should be arranged such that the individual therapeutic agents dissolve independently of one another, *i.e.*, dissolution should occur at approximately the same rate as would occur if the drugs were given separately. In this context, "approximately the same rate" indicates that the time for complete dissolution of agent when drugs are given in the combination tablet should require the same amount of time  $\pm 10\%$  as when the same amount of agent is given alone. This can be achieved by placing the individual layers in a side-by-side arrangement, as opposed, for example, in a single layer tablet matrix containing both agents or one layer forming a core surrounded by the other layer. In a preferred embodiment, the layers are arranged so that they are juxtaposed symmetrically along a single planar surface such that essentially all of the triptan-containing layer is on one side of the plane and essentially all of the NSAID-containing layer is on the other side.

The present claims require that naproxen and triptan be in a tablet in which they are segregated from one another in a "side by side arrangement" and in which their dissolution occurs independently of one another. The claims are limited to one very specific tablet architecture. Among the dosage forms falling outside the claims are: admixtures; any dosage forms other than tablets; tablets in which one drug is in a core and surrounded by a layer or coating containing the second drug; and tablets containing multiple drug release pellets or microparticles. Applicants submit that there is nothing in the prior art that would lead one of skill to choose the claimed dosage form over many other possible choices. As such, the claims at least meet the novelty requirement for patentability.

In order to meet the nonobviousness requirement, a selection invention cannot be simply an arbitrary choice. Thus, to be patentable, there must be some advantage in the specific dosage form that Applicants have claimed that sets it apart from other dosage forms that could have been chosen. Such an advantage is, in fact, demonstrated in the Examples section of the application. Example 1 describes the making of a bilayer tablet that falls within the scope of the present

claims as well as two dosage forms that do not: a tablet in which sumatriptan is in a film coat surrounding naproxen and a tablet in which naproxen and sumatriptan are in admixture. The dissolution characteristics of these tablets are then compared in Example 2.

The rate at which naproxen is released from the different tablets is shown in Table 6 (page 14 of the application) and the rate at which sumatriptan is released is shown in Table 7 (page 15 of the application). The results demonstrate that naproxen is released much more rapidly from the bilayer tablet (see results in Table 6 for the first 30 minutes). In addition, sumatriptan is also released more rapidly from the bilayer tablet, even when compared to the tablet in which sumatriptan is located in an outer coating (see Table 7). Since the claimed drug combinations would be used in treating patients for pain, especially pain associated with migraine headache, the rate at which drugs are released after ingestion by a patient is a very important consideration, and the claimed dosage forms are thus clearly superior to the other tested formulations. The advantages also extend to dissolution following storage (see Tables 8 and 9), stability (see Table 10) and pharmacokinetic characteristics of the claimed dosage form, as described in Example 3.

Applicants acknowledge that Swintowsky disclosed a bilayer dosage form similar to that which is claimed in the present invention, but note that Swintowsky was endeavoring to combine different formulations of a single drug in a single dosage form. Applicants are by contrast combining two separate drugs in a single dosage form, where both drugs are formulated for immediate release. Whyte discloses a bilayer dosage form in which two chemicals which are reactive with each other are arranged to have minimal contact with each other. Applicants are not attempting to prevent reaction of two chemical entities, but rather to provide for superior release characteristics. Thus, the particular references cited by the Examiner do not appear to Applicant to be directly relevant to the present invention.

In light of the results discussed above, Applicants submit that the claimed tablet arrangement does not represent an arbitrary selection. It produces a tablet that has dramatically

improved dissolution characteristics compared to other dosage forms. Moreover, there is nothing in the prior art to suggest the existence this advantage.

The Examiner seems to suggest that one of skill in the art who is developing a drug combination would try many different ways of delivering the drugs and many different dosage forms. However, the existence of an incentive to experiment with different dosage forms is irrelevant to the issue of obviousness. If one dosage form is found to be unexpectedly superior to others, it may be patentable regardless of how it is discovered. In this regard, it should be noted that 35 USC § 103 expressly states: "Patentability shall not be negated by the manner in which the invention was made."

### Conclusion

In light of the amendments and discussion above, Applicants respectfully submit that all of the Examiner's rejections have been overcome. It is therefore requested that these rejections be withdrawn and that the claims presently pending in the application be allowed.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicant's undersigned attorney at (240)864-0915.

Respectfully submitted,

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