

Lab 5

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**UNITED STATES PATENT AND TRADEMARK OFFICE  
CERTIFICATE OF CORRECTION**

PATENT NO. : 6,489,346  
DATED : December 3, 2002  
INVENTOR(S) : Phillips, J.O.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 36

Line 51, after Table 3, please insert Tables 4 and 5 as follows:

**--TABLE 4**

The average length of treatment was 9 days. Cost of care was calculated from these days.

		Per Day	Total
<u>OMEPRAZOLE (day 1)</u>			
Product acquisition cost	40 mg load x 2 5.66/dose)	11.32	11.32
Ancillary product	materials for solution preparation	0.41	0.41
Ancillary product	syringe w/needle	0.20	0.40
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time (\$24/hr)	21 minutes/day (includes pH monitoring)	8.40	8.40
<u>OMEPRAZOLE (days 2-9)</u>			
Product acquisition cost	20 mg per day	2.80	22.65
Ancillary product	materials for solution preparation	0.41	0.82
Ancillary product	syringe w/needle	0.20	1.60
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time (\$24/hr)	18 minutes/day (includes pH monitoring)	8.40	57.60
2/75 patient require 40 mg simplified <u>omeprazole</u> solution per day (days 2-9)			0.63
No additional cost for adverse effects or for failure			
TOTAL		113.43	
Simplified Omeprazole Solution cost per day		12.60	

Pharmacoeconomic evaluation of omeprazole cost of care

MAILING ADDRESS OF SENDER:

Joseph A. Mahoney  
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**TABLE 5**

Time	Control	1 hour	24 hour	2 day	7 day	14 day
Conc (mg/ml)	2.01	2.07	1.94	1.96	1.97	1.98

Stability of Simplified Omeprazole Solution at room temperature  
(25° C.). Values are the mean of three samples.--

Column 37

Line 14, delete "bicarbonate." and insert --bicarbonate;--, therefor.

Line 63, after "plasma will then", insert --be--, therefor.

Column 38

Line 11, delete "Choco-Base" and insert --Choco-Base<sup>TM</sup>--, therefor.

Line 12, after "suspension and", delete "190" and insert --100--, therefor.

Column 39

Line 22, after "suspension and", delete "190" and insert --100--, therefor.

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Claim 1

After "an enantiomer, isomer," insert --derivative--, therefor.

Column 2

Line 17, delete "cimetidine" and insert --Cimetidine--, therefor.

Line 19, delete "39" and insert --30--, therefor.

Line 41, delete "64" and insert --84--, therefor.

Line 48, delete "Antacids" and insert --antacids--, therefor.

Line 63, delete "64" and insert --84--, therefor.

Column 9

Line 42, delete "Brunton" and insert --Goodman AG, et al.--, therefor.

Lines 43-44, delete "In Goodman A G, et al." and insert --in--, therefor.

Column 13

Line 31, delete "inhibitor" and insert --inhibitors--, therefor.

Column 20

Lines 32-33, after "Dextrose 10 mg" insert a new line as follows: --Calcium Hydroxide  
10 mg--

Column 22

Lines 51-52, delete "Choco-Base," and insert --Choco-BaseTM"--, therefor.

Line 56, delete "Choco-Base" and insert --Choco-BaseTM--, therefor.

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INVENTOR(S) : Phillips, J.O.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 23

Line 29, after "males and 6" insert --were--, therefor.

Column 24

Line 21, delete "Choco-Base" and insert --Choco-BaseTM--, therefor.

Column 28

Line 39, delete "Choco-Base" and insert --Choco-BaseTM--, therefor.  
Line 46, delete "Choco-Base" and insert --Choco-BaseTM--, therefor.  
Line 55, delete "Choco-Base" and insert --Choco-BaseTM--, therefor.

Column 36

Line 30, after "TOTAL", delete --far-- and insert --for--, therefor.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Phillips, J.O. ) ATTORNEY DOCKET: 01723326  
 )  
 PATENT NO.: 6,489,346 ) GROUP ART UNIT: 1625  
 )  
 FILED: January 11, 2000 ) EXAMINER: Fan, J.  
 )  
 TITLE: Substituted Benzimidazole Dosage Forms and Method of Using Same  
 )  
 CUSTOMER NO.: 26565

**DECLARATION OF DAVID C. YEOMANS, Ph.D. IN SUPPORT OF APPLICATION FOR PATENT TERM EXTENSION**

I, David C. Yeomans, Ph.D., declare:

1. I am the Director of the Stanford Pain Research Center and on the Faculty of the Department of Anesthesia at Stanford University School of Medicine in Stanford, California. I make the statements in this Declaration from my own personal knowledge, and if required, could and would testify competently to the facts contained herein.

**Background and Experience**

2. I have a Doctoral degree in Neuroscience from University of Florida and a Bachelor of Arts degree in Psychology from Dartmouth College. I also did a Post-doctoral fellowship in Pharmacology at the University of Illinois. A true and correct copy of my Curriculum Vitae is attached as Exhibit A.

3. In my role as Director of the Stanford Pain Research Center, I provide guidance and coordination of pharmacologic research relevant to anesthesia and pain across Stanford University. This work includes the development and use of novel models to help understand how pain in different body systems works, and how best to therapeutically

manipulate these mechanisms. This work further includes extensive analysis of the pharmacological interactions among various drugs and drug combinations.

4. As part of my investigations relating to drug interactions, I discovered an important synergy in the analgesic effects of N-type calcium channel blockers and morphine as more fully described in my publication titled "Combined Effects of N-type Calcium Channel Blockers And Morphine On A-delta vs. C Fiber Mediated Nociception," a copy of which is attached as Exhibit B. This particular discovery has provided me with an understanding of the methodologies and analysis necessary to distinguish pharmacologic synergies from those drug interactions that are not synergistic.

5. A subset of the general field of pain research is the specific research relating to gastric acidity induced pain. In animal models, I have routinely conducted research relating to the pharmacologic inhibition of pain induced by injection of noxious chemicals into the gastric cavity. This experience has provided me with substantial working knowledge of pain and pain inhibition with gastric tissue.

### **Undertaking**

6. Due to my extensive pharmacology background, and more specifically to my experience with pharmacological interactions, I have been asked to determine whether a synergistic effect and/or other pharmacological interaction results from the combination of the proton pump inhibitor, Omeprazole<sup>1</sup>, and an antacid Buffer<sup>2</sup>.

---

<sup>1</sup> "Omeprazole" as used in this Declaration is 40 mg of uncoated or "naked" omeprazole (*i.e.*, not enteric coated).

<sup>2</sup> "Buffer" as used in this Declaration is 20 mEq of sodium bicarbonate or 30 mEq of a 1:1 mixture of sodium bicarbonate and calcium carbonate. I refer to Omeprazole and the Buffer individually in this Declaration as a

## Summary of Conclusions

7. For the reasons provided in this Declaration, I have concluded that the combination of these two Compounds produces a pharmacological interaction. Furthermore, I have concluded that this interaction is synergistic.

8. With regard to my conclusion that a synergistic effect exists for the combination of the Compounds, I specifically conclude that the effect of the combination of the two Compounds was greater than the sum of their predicted individual acid reducing effects. In fact, for the Compounds tested, the acid reducing effects for the combination was supra-additive when compared to the sum of the effects of each Compound administered alone (see Figure 1 below). Thus, when the Omeprazole was co-administered with the Buffer to adult volunteers, the resultant data demonstrated a 500% (5-fold) increase in the acid reducing effect of the combination over the sum of the effects of Omeprazole the Buffer alone.

9. With regard to my conclusion that a pharmacological interaction exists for the combination of the Compounds, I specifically conclude that the effect of the combination of the Compounds described in the paragraph above is an example of a pharmacological interaction for two reasons. First, the administration of the Buffer influences acid reducing effects of administration of the Omeprazole. Second, for the reasons provided above that show a synergistic effect between the two Compounds, I also conclude that a pharmacological interaction is inherently present if there is a finding of synergy.

---

“Compound” and collectively as “Compounds.” It is also my understanding that the combination of the Omeprazole and the Buffer comprise the product known as Zegerid™.

## Definitions

10. Before explaining the analysis I performed in reaching my conclusions above, I first provide generally accepted definitions for synergy and pharmacological interaction, as are well known by pharmacologists such as myself.

11. Synergy has a very specific meaning in pharmacology. The phenomenon of *synergy* is understood to mean that if the *measured* effects of a combination of two drugs are greater than that *predicted* by the sum of the effects of the individual drugs, the combination is considered to be *synergistic*. Synergy may be explained by reference to a number of variables that are analyzed using three steps: a measured effect step, a predicted effect step, and a statistical analysis of the results of these two steps.

12. For the measured effect step, three variables must be experimentally measured for two drugs, A and B: (i) measured effect of drug A (Variable A); (ii) measured effect of drug B (Variable B); and (iii) measured effect of the combination of drug A and drug B (CM).

13. For the predicted effect step, A is added to B resulting in a predicted (additive) combined effect (CP).

14. For the statistical analysis step, CM is compared to CP to determine whether CM is significantly greater than CP. If the statistical analysis shows that CM is statistically significantly greater than CP, then synergy exists by the combination.

15. By way of example, if a dose of drug X produces variable A of 2, and a dose of drug Y produces a variable B of 3, then we would expect that combining these two doses

of the two drugs would produce a CP of 5 ( $2 + 3 = 5$ ). Thus, the pharmacologic interaction between the two drugs would be considered *additive*. On the other hand, if the measured effect (CM) of these two doses of the two drugs produces an effect that is statistically significantly greater than 5, say a CM of 20, then the combination of these two drugs can be considered to form a pharmacologic *synergy*.

16. There are several mathematical models for examining data for synergy, but all have similar underlying principles. See, e.g., Tallarida, Drug Synergism and Dose-Effect Data Analysis, Boca Raton: CRC Press, 2000. Specifically, these models look to see if the experimental results of combinations of two drugs are significantly greater than the predicted result of that same combination. Procedurally, synergy may be determined by conducting certain statistical analyses of experimental data using standard computer statistical applications as described further below.

17. Pharmacological interaction is a more broadly defined term than synergy. Pharmacological interaction describes a condition where the effect of one drug on a body is influenced by the co-administration of another drug on the same body. Some examples of the types of pharmacological interaction include sub-additive, additive and supra-additive (synergistic) effects of the drugs where the two or more drugs have a similar (i.e. overt) general effect on the body.

18. With these general definitions in mind, I now explain the analyses performed in reaching the conclusions above.

## Background Information Related To Analysis Performed

19. I conducted this analysis in my office at Stanford University School of Medicine in Stanford, California.

20. I began my analysis by reviewing experimental data, protocols from pilot studies and other studies ("Pre-NDA Information") collected as part of an NDA application to the Food and Drug Administration for the product Zegerid™. This Pre-NDA Information had already been collected during development of this product and the tests were not performed solely for my analysis below.

21. In addition to the Pre-NDA Information, I also independently reviewed scientific literature relevant to the scope of this analysis.

22. After reviewing the Pre-NDA Information and the relevant scientific literature, I focused my analysis on experimental protocols and data from the Pre-NDA Information, as well as the following particular items:

- a. U.S. Patent Nos. 6,699,885, 6,645,988, 6,489,346, and 5,840,737 attached as Exhibit C.
- b. Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. *Chest*, 2000; 117:260-267 attached as Exhibit D.
- c. Pilbrant A, Cederberg C. Development of an oral formulation of omeprazole. *Scand J Gastroenterol Suppl.* 1985;108:113-20 attached as Exhibit E.

- d. Kaunitz JD, Akiba Y. Duodenal intracellular bicarbonate and the 'CF paradox'. *J. Pancreas*, 2001 Jul;2(4 Suppl):268-73 attached as Exhibit F.
- e. Thomson AB, Pinchbeck B, Kirdeikis J, Kirdeikis P, Zuk L, Brunet MK, Jurima-Romet M, Murray PE, Evaluation of antacid tablets and liquid in fasting and fed men and women. *Clin Ther.* 1988;10(2):158-68 attached as Exhibit G.
- f. Fordtran JS, Morawski SG, Richardson CT. In vivo and in vitro evaluation of liquid antacids. *N Engl J Med.* 1973 May 3;288(18):923-8 attached as Exhibit H.

23. From these items, the following experimental parameters are noted as relevant factors for the analysis.

24. First, in all the experiments that I relied upon, healthy human volunteers were used. At least seven (7) subjects were tested for each drug/group. My experience in pharmacologic testing indicates that this sample size is adequate for the analysis performed.

25. Second, the Compounds were administered orally.

26. Third, all experimental data that I relied upon was from unfed (fasted or premeal) subjects.

27. Fourth, during the course of the experiments that I relied upon, gastric pH was measured at various time points prior to and after administration of the Compounds. Gastric pH is an appropriate endpoint to evaluate acid neutralizing capacity of acid reducing formulations. In some cases, data had been converted to integrated gastric acidity (IGA) in mmol.hr/L (also an appropriate endpoint), prior to my receiving the data. In those cases

where data was sent in raw pH format, I converted this data to IGA to allow direct comparison. To do this, I used the same formula as used throughout the Pre-NDA Information that I relied upon. The formula is as follows:

$$\text{Acid Concentration (mM)} = 1000 \times 10^{-\text{pH}}$$

$$\text{IGA} = (\text{Acid Concentration at time "t}_0\text{"} + \text{Acid Concentration at time "t}_1\text{"}) / 2 \times (t_0 - t_1)$$

Thus, IGA was used to indicate gastric acidity at different time points.

### Analysis

28. With these parameters in mind, I conducted the analysis described below. The object of the analysis was to statistically compare (i) the *measured* acid reducing effect (CM as defined above) of a combination of Omeprazole and the Buffer to (ii) the *predicted* acid reducing effect (CP as defined above) of the same combination based on the sum of the effects of the two Compounds administered alone (A + B).

29. In order to assess, statistically, whether the interaction observed between the two Compounds met the requirements of pharmacologic synergy, data had to be re-expressed as "difference scores." That is, in order to be able to directly compare acidity effects produced by different Compounds, the effect of the Compounds needed to be converted to a value normalized by subtracting a "control value," in this case the last pre-drug acidity value. Thus, for any given time point, these difference scores give a true assessment of acid reducing efficacy of a treatment. Difference scores were therefore created from measured acidity after administering each of the two Compounds alone or administering the combination of the Compounds together. The measured difference scores for the combination of Compounds are referred to as the "Measured Combination Values".

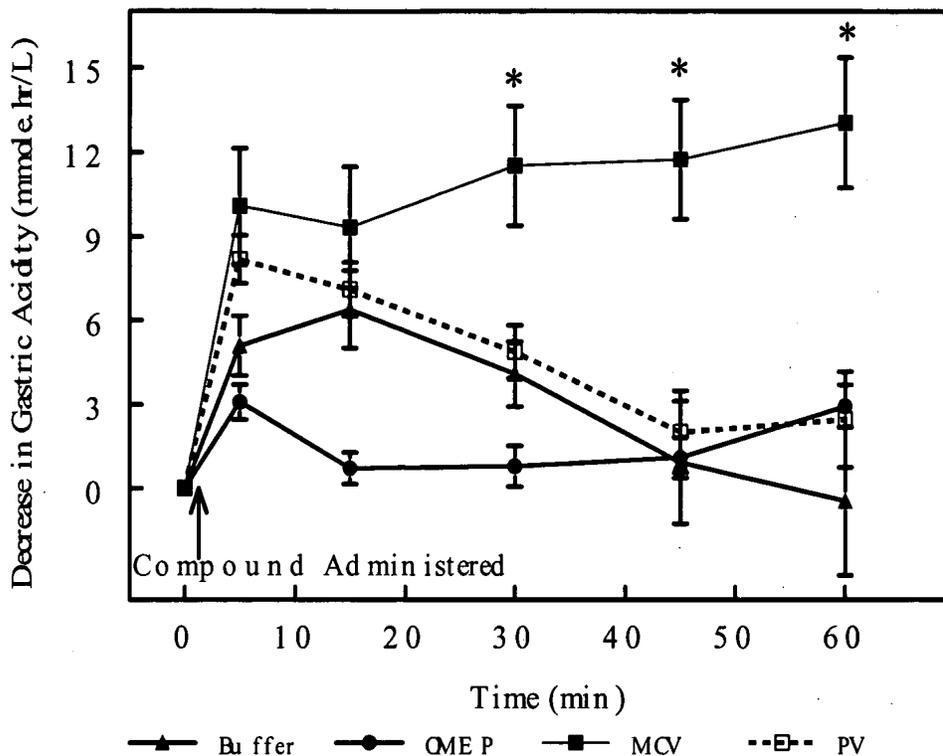
30. Furthermore, by combining measured difference scores obtained from data measured after separate administration of either Compound, I calculated the *predicted* effect of a combination of the two by simply adding the two sets of difference scores (“Predicted Values”).

31. The Predicted Values then were statistically compared to the Measured Combination Values.

32. Statistical analysis was performed to determine if there was an overall significant difference between Predicted Values of the Omeprazole/Buffer combination and the Measured Combination Values using a two-way Analysis of Variance with “predicted vs. measured” and “time after dose” as dependent variables. For this analysis, significance was set at  $p < 0.05$ ; in other words, there is a less than a 5% chance that the results of the analysis occurred randomly. If the Analysis of Variance indicated that the Measured Combination Values were significantly greater than the Predicted Values, the combination of the Compounds were considered synergistic. Follow up analyses were made using a Bonferroni’s test (a well known statistical test) to look for significant differences at particular time points after administration of the Compounds.

## Results

Figure 1. Difference Scores for Actual and Predicted Gastric Acidity



33. Figure 1 shows the difference scores for: (i) the Measured Values<sup>3</sup> of the two Compounds alone; and (ii) the Measured Combination Values (filled squares; MCV) of the combined Compounds. From Figure 1, it is clear that the acid reducing effects of the Buffer alone (filled triangles; Buffer), though robust, are short-lived; the effect of Omeprazole alone (filled circles; OMEP) is fairly minimal; while the effects of the combination of the Compounds (Measured Combination Values) are large, and long lasting.

34. Also in Figure 1, I show the Predicted Values (open squares with broken line; PV) resulting from the simple addition of the Buffer alone value and the Omeprazole alone value (the Measured Values). In examining this Figure, it is clear from its appearance that overall, the actual acid reducing effects of the co-administration of Omeprazole and Buffer

<sup>3</sup> Difference scores for the individual Compounds.

produced substantially greater IGA difference scores than was predicted by the efficacy of the individual Compounds.

35. The impression of a greater than Predicted Value of the combination of Omeprazole and Buffer was confirmed by statistical analysis. The analysis of variance demonstrated an overall significant difference between the Predicted Values and the Measured Combination Values of the two Compounds with a significance level of  $p < 0.05$ .

36. Furthermore, when individual time point data were analyzed, the actual IGA difference score mean was statistically significantly greater at three later time points (30, 45, and 60 min after drug administration), with individual  $p$  values of  $< 0.05$ ,  $< 0.001$ , and  $< 0.001$ , respectively. This means that, for example, there is less than a 1 in 1,000 chance that the differences seen at 60 minutes occurred randomly, rather than by synergy. Thus, this difference between the Predicted Values and Measured Combination Values provides clear, strong statistical evidence of *synergy*.

37. It is also worth noting that the trend of higher Measured Combination Values than Predicted Values holds for the two earliest time points, although these differences did not meet the test of statistical significance. In Figure 1, statistically significantly different individual means are denoted by asterisks (\*).

### **Conclusions**

38. The results of this analysis clearly demonstrate that both the Buffer and Omeprazole are capable of producing acid reducing effects on gastric contents. When administered alone, however, the Buffer has a robust, but short lived acid reducing effect,

and the Omeprazole produces a minimal acid reducing effect, probably due to its instability in acidic solution.

39. Overall, the combination of the Omeprazole and Buffer demonstrated unpredicted supra-additivity on stomach acidity when compared to the Predicted Values of the two Compounds in combination. Examination of individual means at different time points indicates that this difference is not as significant at early time points, probably due to the fact that the Buffer has a very robust acid reducing effect, which brings the stomach to near neutral levels during these early time points. However, at later time points, the robust synergy becomes clearly evident. In fact, within 60 minutes after administering the two Compounds together, the acid reducing effect was *5 fold* greater than that which would be predicted based on the individual effects of the Compounds.

40. In my opinion, therefore, the supra-additivity demonstrated for the combination of Omeprazole and Buffer provides clear evidence of a synergy. Likewise, for these same reasons, I find that the combination of Omeprazole and Buffer provides clear evidence of a pharmacological interaction.

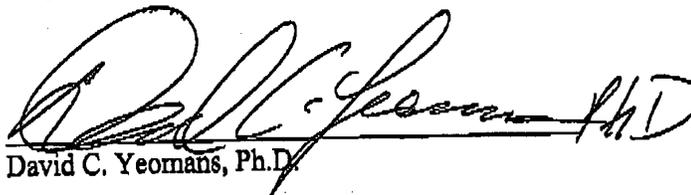
41. It should be noted that for the study from which the Measured Combination Values (filled squares in Figure 1) were derived, 20 mEq of buffering agent was used, whereas in the Buffer alone study (filled triangles in Figure 1) 30 mEq of Buffer was used. It is even more surprising, therefore, that such a large difference in gastric acidity is observed between the Measured Combination Values and the Predicted Values. I would expect that, had the formulation used in the measured combination study contained 30 mEq of Buffer, an even greater difference in gastric acidity would be observed between the Measured

Combination Values and the Buffer alone values, thereby providing even stronger evidence of synergy.

42. Although I analyzed data relating to 40 mg Omeprazole and the Buffer amounts described (*i.e.*, 20 mEq and 30 mEq), all of my conclusions relating to the synergy and pharmacological interaction are equally applicable to a formulation such as Zegerid™ which comprises, *inter alia*, 20 mg Omeprazole and 20 mEq of sodium bicarbonate.

43. The statements made herein are made of my own personal knowledge and are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize any patent term extension which may be granted.

44. Executed this 12 day of August, 2004, in Palo Alto, California.



David C. Yeomans, Ph.D.

Date: August 12, 2004