

09,481,207 *D-1*

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  
 DATE: February 28, 2005 CUSTOMER NO.: 26565

**Certificate of Mailing by "Express Mail"**

"Express Mail" mailing label No. EV300809493US. Date of Deposit: February 28, 2005.  
 I hereby certify that this paper (and its recited enclosures) or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Commissioner for Patents, MAIL STOP: Patent Extension., P.O. Box 1450, Alexandria, VA 22313-1450.

Timothy Hubalik

(signature of person mailing paper or fee)

(typed name of person mailing paper or fee)

Commissioner for Patents  
 MAIL STOP: PATENT EXTENSION  
 P.O. Box 1450  
 Alexandria, VA 22313-1450

Dear Sir:

**REQUEST FOR RECONSIDERATION**

Applicant hereby requests reconsideration of the PTO's "Notice of Final Determination" dated August 30, 2004 in relation to the above-captioned patent. This Request is timely filed pursuant to 37 CFR 1.136, and Applicant has enclosed a check for \$1590 to cover the fee for extension. If additional fees are required, authorization is hereby made to charge such fees to Deposit Account 13-0019.

The PTO bases its determination of ineligibility on two arguments: (1) "the approval of Zegerid™ was not the first permitted marketing or use of either the active ingredient thereof, omeprazole and sodium bicarbonate"<sup>1</sup>; and (2) Despite Applicant's showing of synergy, the

<sup>1</sup> PTO's Notice of Final Determination at p. 2.

Federal Circuit's decision in *Arnold Partnership v. Dudas*, 70 USPQ2d 1311 (Fed. Cir. 2004) precludes an extension based on synergy. Applicant's response to each argument is set forth below. In addition, in Section C below, Applicant provides another basis upon which its application should be granted.

Applicant incorporates herein by reference its Application for Patent Term Extension dated August 12, 2004 as if fully set forth herein (hereinafter "Application").

**A. FDA's Approval of Zegerid™ was the First Permitted Marketing or Use of Immediate-Release Omeprazole Formulation**

Applicant submits that the PTO is incorrect in assuming that there is no difference between Prilosec® (enteric-coated, delayed-release omeprazole) and Zegerid™ when applying 35 U.S.C. §156(f). As detailed in the Application, there are significant differences between these products. Prilosec® is enteric-coated and the omeprazole is not released from the dosage form until it reaches the duodenum where the higher pH causes the dissolution of the enteric coating resulting in the delayed-release characteristic of this product. In contrast, the omeprazole in Zegerid™ is immediately available upon oral ingestion with absorption of omeprazole starting in the stomach. This difference is supported by the pharmacokinetic evidence, which shows that the omeprazole serum concentrations rise much more rapidly for Zegerid™ in the first 45 minutes after dosing as compared to Prilosec®. The invention embodied in the Zegerid™ product is therefore a marked advance for patients in need of rapid absorption. Thus, comparing Zegerid™ to Prilosec® while disregarding the delayed release effect of Prilosec's® enteric-coating, is improper.

Indeed, Applicant submits that it is inappropriate for the PTO to rely on *Arnold Partnership v. Dudas* for the proposition that there is no difference between the hydrocodone/ibuprofen combination of that case and the omeprazole/sodium bicarbonate combination of the present case. Significantly, in the *Arnold* case, there was no issue, like here, regarding the use of non-enteric-coated drug, nor does it appear that the record before the court contained any evidence of synergy. Hydrocodone and ibuprofen were both previously and separately approved in tablet form and therefore in substantially the same form as the combination Vicoprofen®. That is simply not the case with Zegerid™, as detailed above.

The present case is highly similar to the facts of *Glaxo Operations UK Ltd. V. Quigg*, 894 F.2d 392 (Fed. Cir. 1990). In *Glaxo*, the Federal Circuit held that the patent holder was entitled

to an extension for cefuroxime axetil for oral use even though two salts of cefuroxime had been previously approved for intravenous and intramuscular use. *Id* at 393-96. It is undisputed that as among the dosage forms at issue in *Glaxo* (oral, IV and IM), the drug active in the blood is identical – cefuroxime. Thus, the holding hinged on the differences in dosage form and the use of an ester (axetil) to deliver the acid cefuroxime to the bloodstream. Until the ester was discovered, cefuroxime was not orally bioavailable. Intrinsic to the *Glaxo* holding is that the cefuroxime axetil for oral use was a previously unapproved “active ingredient” under §156(f). The Federal Circuit in *Glaxo* rejected the PTO’s argument that §156 only applies to new chemical entities. *Id* at 397.

Likewise, Zegerid™ is a previously unapproved active ingredient for the purposes of §156(f) because of the substantial differences in pharmacokinetics and pharmacodynamics compared to Prilosec®. Stomach absorption of omeprazole via Zegerid™ is different from duodenal absorption via Prilosec®, just as absorption of IM cefuroxime sodium is different from gastrointestinal absorption of cefuroxime axetil. Zegerid™ contains a synergistic amount of sodium bicarbonate and further distinguishes it from the active ingredient in Prilosec®. Without the sodium bicarbonate, the acid-labile omeprazole is destroyed by the stomach acid. That is the reason why Prilosec® uses an enteric coating—to preserve bioavailability. Zegerid’s™ use of sodium bicarbonate together with non-enteric-coated omeprazole is directly analogous to cefuroxime axetil, which was granted an extension. Therefore, the PTO’s present position as to Zegerid™ is without merit and reconsideration is respectfully requested.

**B. The PTO is Improperly Relying on Non-Binding Dicta to Support its Position that Synergy is Irrelevant**

The Federal Circuit’s statements in *Arnold Partnership v. Dudas* (which is not an en banc decision) about synergy were not necessary to the determination of the issues before it and, therefore, are dicta. As such, the PTO should not depart from its position in the MPEP that synergy can provide a basis for patent term extension. The court in *Arnold* did not consider any evidence of synergy and, thus, *Arnold* has no *stare decisis* effect whatsoever. The law is clear that dicta cannot be relied upon in subsequent rulings. *See Loveladies Harbor, Inc. v. U.S.*, 27 F.3d 1545, 1549 (Fed. Cir. 1994). *See also, Humphrey’s Ex’r v. U.S.*, 55 S. Ct. 869, 873 (1935). Consequently, the PTO cannot rely upon *Arnold’s* dicta about synergy.

C. **This is the First Permitted Commercial Marketing or Use of the Product Under the Provision of Law Under Which Such Regulatory Review Period Occurred**

35 U.S.C. § 156(5)(A) provides that (emphasis added):

except as provided in subparagraph (B) or (C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product *under the provision of law under which such regulatory review period occurred*;

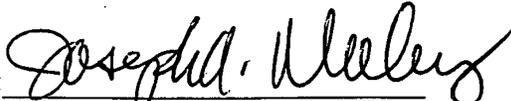
The NDA leading to approval of Zegerid™ was submitted pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. Upon information and belief, none of the NDAs or ANDAs previously approved for omeprazole were filed and thus reviewed under section 505(b)(2). For example, it appears that the full NDAs previously filed were filed (and thus reviewed) under section 505(b)(1) while the approved ANDAs are believed to have been filed and reviewed under section 505(j). Each of these are distinct and separate *provisions of law under which regulatory review occurred*. Therefore, Santarus' NDA 21-636 resulted in the first permitted commercial marketing or use of the product *under the provision of law under which such regulatory review period occurred*, namely, 505(b)(2). For the PTO's convenience, Applicant has attached a listing of omeprazole approvals as shown on FDA's website. For at least this reason, then, Applicant's application for extension should be granted.

D. **Conclusion**

For the foregoing reasons, Applicant's Application for Patent Term Extension should be granted. Applicant requests favorable notification to that effect. Should the PTO have any questions concerning this matter, the PTO is encouraged to contact the undersigned.

Respectfully submitted,

MAYER, BROWN, ROWE & MAW LLP

By:   
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**Enclosures: Listing of omeprazole approvals from the FDA website.**

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## Overview

<b>Drug Name</b>	<b>OMEPRAZOLE</b>
<b>Active Ingredient(s)</b>	• OMEPRAZOLE
<b>Form(s) and Strength(s) Available</b>	• CAPSULE, DELAYED REL PELLETS; ORAL:10MG ;20MG ;40MG • Capsule, Delayed-Release:40MG • Capsule; Oral:10MG ;20MG

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
<a href="#">OMEPRAZOLE (ANDA # 075347)</a>	CAPSULE, DELAYED REL PELLETS; ORAL	Multiple Strengths	Prescription	ANDRX PHARMACEUTICALS
<a href="#">OMEPRAZOLE (ANDA # 075347)</a>	CAPSULE, DELAYED REL PELLETS; ORAL	40MG	None (Tentative Approval)	ANDRX PHARMACEUTICALS
<a href="#">OMEPRAZOLE (ANDA # 075791)</a>	CAPSULE, DELAYED REL PELLETS; ORAL	Multiple Strengths	Prescription	EON
<a href="#">OMEPRAZOLE (ANDA # 075268)</a>	Capsule; Oral	Multiple Strengths	None (Tentative Approval)	GENPHARM
<a href="#">OMEPRAZOLE (ANDA # 075785)</a>	CAPSULE, DELAYED REL PELLETS; ORAL	Multiple Strengths	Prescription	IMPAX LABS
<a href="#">OMEPRAZOLE (ANDA # 075785)</a>	Capsule, Delayed Rel Pellets; Oral	40MG	None (Tentative Approval)	IMPAX LABS
<a href="#">OMEPRAZOLE (ANDA # 075410)</a>	CAPSULE, DELAYED REL PELLETS; ORAL	Multiple Strengths	Prescription	KREMEF URBAN DEV
<a href="#">OMEPRAZOLE (ANDA # 075757)</a>	CAPSULE, DELAYED REL PELLETS; ORAL	Multiple Strengths	Prescription	LEK PHARMACEUTICALS
<a href="#">OMEPRAZOLE (ANDA # 075876)</a>	CAPSULE, DELAYED REL PELLETS; ORAL	Multiple Strengths	Prescription	MYLAN
<a href="#">OMEPRAZOLE (ANDA # 075876)</a>	Capsule, Delayed Rel Pellets; Oral	40MG	None (Tentative Approval)	MYLAN
<a href="#">OMEPRAZOLE (ANDA # 076048)</a>	CAPSULE, DELAYED REL PELLETS; ORAL	Multiple Strengths	Prescription	TORPHARM
<a href="#">OMEPRAZOLE</a>	Capsule, Delayed-	40MG	None (Tentative Approval)	TORPHARM

([ANDA # 076048](#))

[Release](#)

[Approval](#)

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## Overview

**Drug Name**                      **PRILOSEC**

**Active Ingredient(s)**        • **OMEPRAZOLE**

**Form(s) and Strength(s) Available**    • **CAPSULE, DELAYED REL PELLETS; ORAL:10MG ;20MG ;40MG**

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

<b>Drug Name and FDA Application Number</b>	<b>Dosage Form/Route</b>	<b>Strength</b>	<b>Marketing Status</b>	<b>Company</b>
<b>PRILOSEC (NDA # 019810)</b>	CAPSULE, DELAYED REL PELLETS; ORAL	Multiple Strengths	Prescription	ASTRAZENCA

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## Overview

**Drug Name**                      **PRILOSEC OTC**

**Active Ingredient(s)**        • **OMEPRAZOLE MAGNESIUM**

**Form(s) and Strength(s) Available**    • **TABLET, DELAYED RELEASE; ORAL:EQ 20MG BASE**

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

<b>Drug Name and FDA Application Number</b>	<b>Dosage Form/Route</b>	<b>Strength</b>	<b>Marketing Status</b>	<b>Company</b>
<b>PRILOSEC OTC (NDA # 021229)</b>	TABLET, DELAYED RELEASE; ORAL	EQ 20MG BASE	Over-the-counter	ASTRAZENCA

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AUG 30 2004

Joseph A. Mahoney, Esq.  
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PO Box 2828  
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In Re: Patent Term Extension  
Application for  
U.S. Patent No. 6,489,346

#37

## NOTICE OF FINAL DETERMINATION

An application for extension of the patent term of U.S. Patent No. 6,489,346 under 35 U.S.C. § 156 was filed in the United States Patent and Trademark Office on August 12, 2004. The application was filed by The Curators of the University of Missouri. Extension is sought based upon the premarket review under § 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA) of a human drug product known by the tradename Zegerid™ having the active ingredients omeprazole and sodium bicarbonate. Zegerid™ (omeprazole and sodium bicarbonate) was approved for commercial use and sale by the Food and Drug Administration (FDA) on June 15, 2004.

A determination has been made that U.S. Patent No. 6,489,346 is **NOT** eligible for patent term extension under 35 U.S.C. § 156 based upon the regulatory review period of Zegerid® (omeprazole and sodium bicarbonate).

A single request for reconsideration of this FINAL DETERMINATION OF INELIGIBILITY may be made if filed by the applicant within TWO MONTHS of the mailing date of this letter. The period for response **may** be extended pursuant to 37 CFR 1.136. See 37 CFR 1.750. A failure to respond to this letter will result in the application papers being placed into the patent file with no further action taken on the application for patent term extension.

As indicated in the application for patent term extension, and as supported by the Food and Drug Administration's web site, both omeprazole and sodium bicarbonate were previously approved for commercial use or sale. For example, on FDA's web site, the document "NDA Approvals for Calendar Year 2004" indicates that Zegerid™ is a new formulation, not that it contains a new active ingredient.

Under 35 U.S.C. § 156(a) a term of a patent which claims a product shall be extended if, *inter alia*, the product has been subject to a regulatory review period before its commercial marketing or use. In addition, under § 156(a)(5)(A):

the permission for the commercial marketing or use of the product . . . is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; (Emphasis added)

Thus, the determination of eligibility of U.S. Patent No. 6,489,346 turns on the provisions in § 156(a)(5)(A) that the permission for the commercial marketing or use is the first permitted commercial marketing or use of the product. The term “product” is defined in 35 U.S.C. § 156(f) as follows:

- (f) For purposes of this section:
  - (1) The term “product” means:
    - (A) A drug product . . .
  - (2) The term “drug product” means the active ingredient of -
    - (A) A new drug, antibiotic drug, or human biological product...including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient. (Emphasis added.)

A patent is only eligible for extension under 35 U.S.C. 156 if an active ingredient claimed by the patent and subject to regulatory review meets the “first commercial marketing” requirement of 35 U.S.C. 156(a)(5)(A). Omeprazole and sodium bicarbonate are separate active ingredients, and are not treated as a single active ingredient merely because they are administered together. Since the approval of Zegerid™ was not the first permitted marketing or use of either the active ingredient thereof, omeprazole and sodium bicarbonate, the patent is not eligible for patent term extension based upon the regulatory review of Zegerid™ (omeprazole and sodium bicarbonate). Arnold Partnership v. Dudas, 70 USPQ2d 1311 (Fed. Cir. 2004) (affirming a decision that U.S. Patent No. 4,587,252 is not entitled to patent term extension based upon the regulatory review and approval of hydrocodone bitartrate and ibuprofen, because both active ingredients had been previously approved for commercial use or sale).

As to applicant’s argument that a showing of synergistic effect should have a bearing upon eligibility for patent term extension, applicant is considered to have established a synergistic effect between the two active ingredients. However, the court in Arnold noted:

This court also addresses briefly whether synergistic combination drug patents qualify for a patent term extension under § 156...Moreover, this court doubts that synergistic effects are an appropriate distinction for term extension policies, particularly where the statutory language does not distinguish at all between synergistic and nonsynergistic combinations. Arnold at 1315.

In view of the Arnold decision, Section 2751 of the Manual of Patent Examining Procedure, Rev. 2, May 2004, will be revised to remove the suggestion that a synergistic effect could have a bearing upon whether a combination product could be considered a single active ingredient for purposes of 35 U.S.C. 156. (This is found in the paragraph spanning pages 2700-31 and 2700-32.)

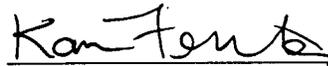
In view of the above, the term of U.S. Patent No. 6,489,346 is not eligible for extension under 35 U.S.C. § 156 based upon the approval of the product Zegerid™ (omeprazole and sodium bicarbonate) and the application for patent term extension, filed August 12, 2004, is dismissed.

Any correspondence with respect to this matter should be addressed as follows:

By mail:                   Mail Stop Patent Ext.  
                              Commissioner for Patents  
                              P.O. Box 1450  
                              Alexandria, VA 22313-1450

By FAX:                   (703) 872-9411 (please contact the undersigned if sending a fax after  
                              September 28, 2004, the fax number may have changed)

Telephone inquiries related to this determination should be directed to the undersigned at (703) 306-3159. (After September 28, 2004, the telephone number should be (571)272-7744.) E-mail inquiries should be directed to [Karin.Ferriter@uspto.gov](mailto:Karin.Ferriter@uspto.gov).



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Karin Ferriter  
Senior Legal Advisor  
Office of Patent Legal Administration  
Office of the Deputy Assistant Commissioner  
for Patent Policy and Projects

Attachment: NDA Approvals for Calendar Year 2004 (Updated through July 31 2004)



# U.S. Food and Drug Administration



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### NDA APPROVALS FOR CALENDAR YEAR 2004

Updated through July 31, 2004

NDA Number	Drug Name	Generic Name	Applicant/Sponsor	Chemical Type	Therapeutic Class	Approval Date
21604	Children's Elixsure IB	Ibuprofen	Taro Pharms	5	S	07-Jan-04
21539	Acetadote	Acetylcysteine	Cumberland Pharms	3	PV	23-Jan-04
21646	Infuvite Pediatric	Multiple Vitamins	Sabex 2002	5	S	29-Jan-04
21395	Spiriva Handihaler	Tiotropium Bromide	Boehringer Ingelheim	1	S	30-Jan-04
21540	Caduet	Amlodipine Besylate; Atrovastatin Calcium	Pfizer	4	S	30-Jan-04
21625	MVI Adult	Multi-Vitamins	aaiPharma	3	S	30-Jan-04
21462	Alimta	Pemetrexed Disodium	Eli Lilly	1	PV	04-Feb-04
21594	Amiodarone Hydrochloride	Amiodarone Hydrochloride	International Medication Sys	5	S	04-Feb-04
21644	Clobex	Clobetasol Propionate	Galderma Labs	3	S	05-Feb-04
21166	Estrogel	Estradiol	Solvay Pharms	3	S	09-Feb-04
21590	Fazaclo	Clozapine	Alamo Pharms	3	S	10-Feb-04
21643	MVI Adult	Multi-Vitamins	aaiPharma	3	S	18-Feb-04
21587	Children's Advil Allergy Sinus	Ibuprofen; Pseudoephedrine Hydrochloride; Chlorpheniramine Maleate	Wyeth Cons	3	S	24-Feb-04
50791	Myfortic	Mycophenolic Acid	Novartis Pharms	2	S	27-Feb-04
21571	Iquix	Levofloxacin	Santen	3	S	01-Mar-04
21688	Sensipar	Cinacalcet Hydrochloride	Amgen	1	P	08-Mar-04
21621	Zyrtec	Cetirizine Hydrochloride	Pfizer	3	S	16-Mar-04
21211	Follistim AQ	Follitropin Beta	Organon	3	S	23-Mar-04
21765	Gonal-F	Follitropin Alfa	Serono Inc	3	S	25-Mar-04
21253	Zyprexa IM	Olanzapine	Eli Lilly	3	S	29-Mar-04
21144	Ketek	Telithromycin	Aventis Pharms	1	S	01-Apr-04
20784	Nasacort HFA	Triamcinolone Acetonide	Aventis Pharms	3	S	07-Apr-04

21256	Human Secretin	Human Secretin	Chirhoclin	1	PV	09-Apr-04
21629	Apidra	Insulin Glulisine	Aventis Pharms	1	S	16-Apr-04
21264	Apokyn	Apomorphine Hydrochloride	Bertek	1	P	20-Apr-04
21574	Fortamet	Metformin Hydrochloride	Andrx	5	S	27-Apr-04
21640	Vitrase	Ovine Hyaluronidase	Ista Pharms	1	P	05-May-04
21504	Lidosite Topical System	Lidocaine Hydrochloride; Epinephrine	Vyteris	3	S	06-May-04
21617	Zalkote	Valproate Sodium	Andrx	3	S	06-May-04
21443	Enjuvia	Synthetic Conjugated Estrogens, B	Duramed	3	S	10-May-04
21551	Halflytely and Bisacodyl Bowel Prep Kit	PEG-3350;Sodium Chloride;Sodium Bicarbonate;Potassium Chloride;Bisacodyl	Braintree	3	S	10-May-04
21433	Flovent HFA	Fluticasone Propionate	GlaxoSmithKline	3	S	14-May-04
21618	Tindamax	Tinidazole	Presutti Labs	1	SV	17-May-04
21671	Depodur	Morphine Sulfate	Skye Pharma	3	S	18-May-04
50794	Vidaza	Azacitidine	Pharmion	1	PV	19-May-04
21361	Xifaxan	Rifaximin	Salix Pharms	1	S	25-May-04
21494	Axid	Nizatidine	Reliant Pharma	3	S	25-May-04
21684	Gonal-F RFF Pen	Follitropin Alfa	Serono Inc	3	S	25-May-04
21566	Prevacid IV	Lansoprazole	Tap Pharm	3	S	27-May-04
21595	Sanctura	Trospium Chloride	Indevus	1	S	28-May-04
21530	Mobic	Meloxicam	Boehringer Ingelheim	3	S	01-Jun-04
21516	Istalol	Timolol Maleate	Senju	3	S	04-Jun-04
21667	NutreSore	L-Glutamine	Nutritional Restart	1	SV	10-Jun-04
21636	Zegerid	Omeprazole	Santarus	3	S	15-Jun-04
21369	Codeprex	Codeine Polistirex;Chlorpheniramine Polistirex	Celltech Pharms	3	S	21-Jun-04
21585	Mucinex D	Guaifenesin;Pseudoephedrine Hydrochloride	Adams	3	S	22-Jun-04
21512	Loratadine	Loratadine	Perrigo	3	S	24-Jun-04
50789	Tobramycin	Tobramycin	American Pharm	5	S	13-Jul-04
21612	Luxacor	Fenofibrate	Cipher	3	S	15-Jul-04
21497	Alinia	Nitazoxanide	Romark	3	P	21-Jul-04
21687	Vytorin	Ezetimibe; Simvastatin	MSP Singapore	4	S	23-Jul-04
21415	Metvix	Methyl Aminolevulinate	PhotoCure ASA	3	S	27-Jul-04
21431	Campral	Acamprosate Calcium	Lipha	1	P	29-Jul-04
	Cefotaxime and Dextrose					

50792	Duplex Container	Cefotaxime Sodium	B Braun	5	S	29-Jul-04
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**Chemical Types:**

- 1 - New molecular entity
- 2 - New ester, new salt, or other noncovalent derivative
- 3 - New formulation
- 4 - New combination
- 5 - New manufacturer
- 6 - New indication (Beginning in 1994, Type 6's were tracked as efficacy supplements, not as NDAs.)
- 7 - Drug already marketed, but without an approved NDA

**Therapeutic Potentials:**

**P - Priority Review** - Significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease.

**S - Standard Review** - The drug appears to have therapeutic qualities similar to those of one or more already marketed drugs.

**V - Orphan Drug**

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Date created: March 5, 2004; updated August 16, 2004



#36

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  
 DATE: August 12, 2004 CUSTOMER NO.: 26565

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Joseph A. Mahoney

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(typed name of person mailing paper or fee)

Commissioner for Patents  
 MAIL STOP: PATENT EXT.  
 P.O. Box 1450  
 Alexandria, VA 22313-1450

**TRANSMITTAL LETTER**

Dear Sir:

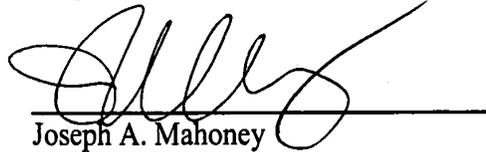
Enclosed herewith are the following for the above-captioned application:

1. Original and two (2) copies of a Patent Term Extension Application for U.S. Patent No. 6,489,346;
2. Declaration of David C. Yeomans, Ph.D., in support of PTE (including Exhibits A - H);
3. Two (2) copies of Certificates of Correction previously filed in U.S. Patent No. 6,489,346;
4. Copy of a Terminal Disclaimer filed in U.S. Patent No. 6,489,346;
5. Copy of USPTO Maintenance Fee Report in U.S. Patent No. 6,489,346;

6. Copy of U.S. Patent No. 6,489,346; and
7. Return receipt postcard.

The Commissioner is hereby authorized to charge the filing fees in the amount of \$1,220.00 to Deposit Account 13-0019 in addition to any other fees that may be required for this filing.

Respectfully submitted,



Joseph A. Mahoney  
Reg. No. 38,956

Date: August 13, 2004

**MAYER, BROWN, ROWE & MAW LLP**

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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
DATE: August 12, 2004 CUSTOMER NO.: 26565

Certificate of Mailing by "Express Mail"

"Express Mail" mailing label No. EL 989698130 US. Date of Deposit: August 12, 2004.
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Joseph A. Mahoney

(signature of person mailing paper or fee)

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Commissioner for Patents
MAIL STOP: PATENT EXT.
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPLICATION FOR PATENT TERM EXTENSION

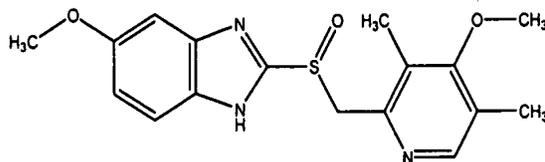
Pursuant to the provisions of 35 U.S.C. § 156, The Curators of the University of Missouri
(hereinafter "Missouri") hereby requests an extension of the term of U.S. Patent No. 6,489,346
(hereinafter the '346 patent) of 433 days, from July 15, 2016 to September 22, 2017. Missouri is
the owner of record of the '346 patent and Santarus, Inc. (hereinafter "Santarus") is the exclusive
licensee of the '346 patent pursuant to an agreement executed on January 26, 2001. Information
used in preparing this application, including the response to 37 C.F.R. § 1.740(a)(4) was
obtained, at least in part, from Santarus.

Applicant hereby provides the following information as required by 37 C.F.R. § 1.740(a):

## Section 1: Complete identification of the approved product.

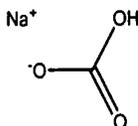
The approved product, Zegerid™ Powder for Oral Suspension, comprises omeprazole (20 mg strength) as an active ingredient, sodium bicarbonate (1680 mg) which acts to protect the omeprazole from acid degradation in gastrointestinal fluids, and several inactive ingredients including sucrose, sucralose, xanthan gum, xylitol, and flavorings.

Omeprazole has the following chemical formula:



and its chemical name is 5-methoxy-2-[[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole. The empirical formula for omeprazole is C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S and its molecular weight is 345.42.

Sodium bicarbonate has the following chemical formula:



The empirical formula for sodium bicarbonate is CHNaO<sub>3</sub> and its molecular weight is 84.01. A copy of the FDA approval letter in regards to Zegerid™ is attached herewith as **Attachment 1**.

According to the Manual of Patent Examining Procedure (“M.P.E.P.”), *Eighth Edition*, Revision 2 (§ 2752, page 2700-32), “an approved product having two active ingredients, which are *not shown to have a synergistic effect or have pharmacological interaction*, will not be considered to have a single active ingredient made of the two active ingredients.” (emphasis added). Therefore, according to the M.P.E.P., an approved drug product having two or more active ingredients, which are shown to have a synergistic effect or a pharmacological interaction should be considered to have a single active ingredient made of the two active ingredients. The term “active ingredient” is defined in the M.P.E.P. (§ 2752, page 2700-31) to be “the ingredient in the drug product that becomes therapeutically active when administered.”

Zegerid™ Powder for Oral Suspension is an immediate-release formulation that contains omeprazole (an acid labile proton pump inhibitor) and sodium bicarbonate which is present, *inter alia*, to raise the pH of the gastrointestinal fluid thereby protecting omeprazole from acid

degradation in the gastrointestinal tract and allowing for absorption of omeprazole in the stomach.

As supported by the Declaration of David C. Yeomans, Ph.D., of Stanford University, submitted herewith and incorporated by reference herein, Applicant has shown both a pharmacological interaction and a synergistic interaction between omeprazole and sodium bicarbonate. *See, e.g.*, Declaration of Dr. David Yeomans at ¶¶ 7-9.

Although the FDA labeling does not indicate that sodium bicarbonate is an active ingredient, this is not dispositive for purposes of patent term extension. Congress has granted to the United States Patent and Trademark Office (“PTO”), not the FDA, the authority to determine whether a patent is eligible for patent term extension under 35 U.S.C. § 156. Therefore, in determining the “active ingredient” of Zegerid™ for purposes of patent term extension, the PTO should not look to what was ultimately listed as the active ingredient on the FDA label, but rather, the PTO should independently determine what constitutes the “active ingredient” for purposes of 35 U.S.C. § 156.

“The Manual of Patent Examining Procedure (MPEP) contains details of the practices and procedures whereby the PTO implements its statutory mission.” *Exxon Corp. v. Phillips Petroleum Co.*, 265 F.3d 1249, 1251 (Fed. Cir. 2001). Again, the M.P.E.P. defines “active ingredient” to be “the ingredient in the drug product that becomes therapeutically active when administered.” (§ 2752, page 2700-31). Applicant hereby submits that it is the *combination* of omeprazole and sodium bicarbonate that becomes therapeutically active for the approved uses of Zegerid™. *See, e.g.*, Declaration of Dr. David Yeomans at Figure 1. In other words, without sodium bicarbonate or another buffering agent as provided by the ‘346 patent, the omeprazole would degrade in the gastrointestinal fluid, thereby significantly decreasing or eliminating altogether its therapeutic effectiveness for the approved uses. *See, e.g., Id.* at ¶¶ 38-39. Therefore, Applicant submits that the PTO should consider both omeprazole and sodium bicarbonate to be active ingredients for purposes of patent term extension and therefore that Zegerid™ has a single active ingredient made up of these two ingredients.

Section 2: Complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355), section 505(b)(2).

Section 3: Identification of the date on which the product received permission for commercial marketing.

Zegerid™ received permission for commercial marketing or use under Section 505(c) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on June 15, 2004.

Section 4: Identification of each active ingredient.

As discussed above and in the Declaration of David C. Yeomans, Ph.D., attached herewith, omeprazole and sodium bicarbonate act together to produce the pharmacological interaction of Zegerid™. For example, without sodium bicarbonate or another buffering agent as provided by the '346 patent, the omeprazole present in Zegerid™ would degrade in gastrointestinal fluid and would not become therapeutically active. As such, the new active ingredient, for purposes of patent term extension under 35 U.S.C. § 156, is a combination of omeprazole/sodium bicarbonate, which has not been previously approved for commercial marketing or use.

It is Missouri's understanding that **enteric coated granules** of omeprazole were first approved for commercial marketing or use under Section 505(c) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on September 14, 1989 (*i.e.* Prilosec®). It is also pointed out that sodium bicarbonate has been approved as an active ingredient in prescription products including, for example, Baros (approved August 7, 1985) and BSS Plus (approved October 28, 1981).

As detailed in the '346 patent and herein, the omeprazole/sodium bicarbonate combination under consideration is markedly different from both the enteric coated granules of Prilosec® and sodium bicarbonate as single agents.

Section 5: Timeframe for submission.

This application is being timely submitted within the sixty-day period provided by 35 U.S.C. § 156(d)(1) since approval was granted on June 15, 2004 and the sixty-day period will expire on Saturday, August 14, 2004.

Section 6 and 7: Compete identification of the patent and copy of the patent.

The patent for which an extension is sought is:

U.S. Patent No.:	6,489,346
Issued:	December 3, 2003
Inventor:	Jeffrey O. Phillips
Filed:	January 11, 2000
Expires:	July 16, 2016

A copy of U.S. Patent No. 6,489, 346 is enclosed herewith as **Attachment 2**.

Section 8: Copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

Enclosed as **Attachment 3** is a schedule of maintenance fee payments (none have yet come due), as **Attachment 4** a copy of a Terminal Disclaimer filed during prosecution of U.S. Patent No. 6,489,346, and as **Attachment 5** two certificates of correction filed regarding U.S. Patent No. 6,489,346.

Section 9: Statement that the patent claims the approved product and a method of using the approved product.

U.S. Patent No. 6,489,346 claims the approved product and methods of using the approved product. The applicable claims of the '346 patent are claims 24, 26, 31-35, 37, 50 – 53, 55 – 60, 65 – 66, 68, 80 – 86, 90 – 94, and 117 – 118. Below, the applicable claims are provided (single space) followed by a brief description explaining how the claim in question embraces the approved product.

**Claims**

**Claim 24.** A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject a solid pharmaceutical composition in a dosage

form that is not enteric-coated; wherein the composition comprises active ingredients consisting essentially of:

(a) a therapeutically effective amount of approximately 5 mg to approximately 300 mg of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and

(b) a buffering agent in an amount of approximately 1.0 mEq to approximately 150 mEq selected from the group consisting of a bicarbonate salt of a group IA metal, a calcium salt, and a magnesium salt, wherein the buffering agent is in an amount sufficient to elevate gastric acid pH of the subject's stomach to prevent or inhibit gastric acid degradation of the non-enteric coated proton pump inhibitor and achieve sufficient bioavailability of the proton pump inhibitor in the subject to elicit a therapeutic effect.

Zegerid™ powder for oral suspension is a non-enteric coated solid dosage form (powder) that comprises 20 mg of powder omeprazole and 20 mEq of buffering agent (sodium bicarbonate), which is a bicarbonate salt of a Group IA metal. The buffering agent is present in an amount sufficient to elevate gastric acid pH of the subject's stomach to prevent or inhibit gastric acid degradation of the non-enteric coated proton pump inhibitor and achieve sufficient bioavailability of the proton pump inhibitor in the subject to elicit a therapeutic effect.

Therefore, claim 24 reads on the approved product.

**Claim 26.** The method of claim 24, wherein the sodium bicarbonate is in an amount from about 1000 mg to about 1680 mg.

The sodium bicarbonate is present in an amount of 1680 mg. Therefore, claim 26 reads on the approved product.

**Claim 31.** The method of claim 24, wherein the buffering agent is in an amount of at least 10 mEq.

The sodium bicarbonate is present in an amount of 20 mEq. Therefore, claim 31 reads on the approved product.

**Claim 32.** The method of claim 24, wherein the buffering agent is in an amount from about 10 mEq to about 70 mEq.

The sodium bicarbonate is present in an amount of 20 mEq. Therefore, claim 32 reads on the approved product.

**Claim 33.** The method of claim 24, wherein the buffering agent is in an amount from about 20 mEq to about 40 mEq.

The sodium bicarbonate is present in an amount of 20 mEq. Therefore, claim 33 reads on the approved product.

**Claim 34.** The method of claim 24, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

The omeprazole is present in an amount of 20 mg. Therefore, claim 34 reads on the approved product.

**Claim 35.** The method of claim 24, wherein the proton pump inhibitor is omeprazole.

The proton pump inhibitor is omeprazole. Therefore, claim 35 reads on the approved product.

**Claim 37.** The method of claim 35, wherein the omeprazole is present in an amount of about 20 mg.

The omeprazole is present in an amount of 20 mg. Therefore, claim 37 reads on the approved product.

**Claim 50.** The method of claim 24, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets, and granules.

The composition is in a powder dosage form. Therefore, claim 50 reads on the approved product.

**Claim 51.** The method of claim 24, wherein the subject is a human.

Zegerid™ powder for oral suspension is approved for the treatment of humans. Therefore, claim 51 reads on the approved product.

**Claim 52.** The method of claim 24, wherein the dosage form further comprises a flavoring agent.

Zegerid™ powder for oral suspension comprises peach and peppermint flavors. Therefore, claim 52 reads on the approved product.

**Claim 53.** The method of claim 52, wherein the flavoring agent comprises aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

Zegerid™ powder for oral suspension comprises peppermint flavor. Therefore, claim 53 reads on the approved product.

**Claim 55.** The method of claim 24, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

Zegerid™ powder for oral suspension is indicated for short-term treatment of active duodenal ulcers, treatment of heartburn and other symptoms associated with GERD, short-term treatment of erosive esophagitis, and to maintain healing of erosive esophagitis. Therefore, claim 55 reads on the approved product.

**Claim 56.** The method of claim 24, wherein the dosage form is administered once or twice a day.

The recommended dose of Zegerid™ powder for oral suspension is 20 mg once daily. Therefore, claim 56 reads on the approved product.

**Claim 57.** A solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising: active ingredients consisting essentially of:

(a) a therapeutically effective amount of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and

(b) a buffering agent selected from the group consisting of sodium bicarbonate, and calcium carbonate, in an amount more than about 40 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

Zegerid™ powder for oral suspension is a non-enteric coated solid dosage form (powder) that comprises 20 mg of non-enteric coated omeprazole (a therapeutically effective amount) and 1680 mg of sodium bicarbonate. The buffering agent is present in an amount of 84 times the amount of the omeprazole on a weight to weight basis. Therefore, claim 57 reads on the approved product.

**Claim 58.** The composition as recited in claim 57, wherein the buffering agent is sodium bicarbonate.

The buffering agent is sodium bicarbonate. Therefore, claim 58 reads on the approved product.

**Claim 59.** The composition as recited in claim 57, wherein the sodium bicarbonate is in an amount from about 400 mg to about 4000 mg.

The sodium bicarbonate is present in an amount of 1680 mg. Therefore, claim 59 reads on the approved product.

**Claim 60.** The composition as recited in claim 57, wherein the sodium bicarbonate is in an amount of at least about 800 mg.

The sodium bicarbonate is present in an amount of 1680 mg. Therefore, claim 60 reads on the approved product.

**Claim 65.** The composition as recited in claim 57, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

The omeprazole is present in an amount of 20 mg. Therefore, claim 65 reads on the approved product.

**Claim 66.** The composition as recited in claim 57, wherein the proton pump inhibitor is omeprazole.

The proton pump inhibitor is omeprazole. Therefore, claim 66 reads on the approved product.

**Claim 68.** The composition as recited in claim 66, wherein the omeprazole is present in an amount of about 20 mg.

The omeprazole is present in an amount of 20 mg. Therefore, claim 68 reads on the approved product.

**Claim 80.** The composition as recited in claim 57, wherein the proton pump inhibitor is micronized.

The omeprazole is present in micronized form. Therefore, claim 80 reads on the approved product.

**Claim 81.** The composition as recited in claim 57, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets, and granules.

Zegerid™ powder for oral suspension is in the form of a powder. Therefore, claim 81 reads on the approved product.

**Claim 82.** The composition as recited in claim 57, further comprising a flavoring agent comprising aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

Zegerid™ powder for oral suspension comprises either peppermint or peach flavoring agent. Therefore, claim 82 reads on the approved product.

**Claim 83.** The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 50 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

The buffering agent is present in an amount of 84 times the amount of proton pump inhibitor on a weight to weight basis. Therefore, claim 83 reads on the approved product.

**Claim 84.** The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 60 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

The buffering agent is present in an amount of 84 times the amount of proton pump inhibitor on a weight to weight basis. Therefore, claim 84 reads on the approved product.

**Claim 85.** The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 70 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

The buffering agent is present in an amount of 84 times the amount of proton pump inhibitor on a weight to weight basis. Therefore, claim 85 reads on the approved product.

**Claim 86.** The composition as recited in claim 57, wherein the amount of the buffering agent is more than about 80 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

The buffering agent is present in an amount of 84 times the amount of proton pump inhibitor on a weight to weight basis. Therefore, claim 86 reads on the approved product.

**Claim 90.** A method of producing a liquid pharmaceutical composition comprising: combining the dosage form of claim 57 with an aqueous medium.

Prior to administering Zegerid™ powder for oral suspension, the powder is to be combined with 2 tablespoons of water. Therefore, claim 90 reads on the approved product.

**Claim 91.** A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject the dosage form as recited in claim 57 via a route selected from the group consisting of oral, nasogastric, and gastric tube.

Zegerid™ powder for oral suspension is indicated for treatment of acid-caused gastrointestinal disorders and is to be administered to orally. Therefore, claim 91 reads on the approved product.

**Claim 92.** The method as recited in claim 91, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

Zegerid™ powder for oral suspension is indicated for short-term treatment of active duodenal ulcers, treatment of heartburn and other symptoms associated with GERD, short-term treatment of erosive esophagitis, and to maintain healing of erosive esophagitis. Therefore, claim 92 reads on the approved product.

**Claim 93.** The method as recited in claim 91, wherein the composition is administered once or twice a day.

The recommended dose of Zegerid™ powder for oral suspension is 20 mg once daily. Therefore, claim 93 reads on the approved product.

**Claim 94.** A method for administering a liquid pharmaceutical composition to a subject, comprising: combining the pharmaceutical composition as recited in claim 57 with an aqueous medium to form a suspension, and orally administering the suspension to the subject in a single dose without administering an additional buffering agent.

Zegerid™ powder for oral suspension is indicated to be combined with two tablespoons of water prior to administration. No additional buffering agent is required. Therefore, claim 94 reads on the approved product.

**Claim 117.** The method of claim 24, wherein the composition further comprises a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

Zegerid™ powder for oral suspension comprises various excipients. Therefore, claim 117 reads on the approved product.

**Claim 118.** The method of claim 24, wherein the composition further comprises a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

Zegerid™ powder for oral suspension comprises various excipients. Therefore, claim 118 reads on the approved product.

Section 10: Relevant dates and information pursuant to 35 U.S.C. 156(g) to enable a determination of the applicable regulatory review period.

- |                      |  |
|----------------------|--|
| 1. November 10, 1994 | Effective date of IND Application No. 46-656.  |
| 2. December 3, 2002  | Date of Issuance of U.S. Patent No. 6,489,346. |
| 2. August 15, 2003   | Submittal date of NDA No. 21-636.              |
| 3. June 15, 2004     | Date of approval of NDA No. 21-636.            |

Section 11: Brief description of the activities undertaken during the applicable regulatory review period with respect to the approved product and significant dates applicable to such activities.

Santarus, the marketing applicant, undertook development of this product to establish, by adequate and well-controlled clinical trials, its safety and effectiveness for short-term treatment of active duodenal ulcer, treatment of heartburn and other symptoms associated with GERD, maintenance of healing of erosive esophagitis, and short term treatment of erosive esophagitis.

The following is a chronology of the activities undertaken by Santarus during the applicable regulatory review period:

**Regulatory Review Period Activities for IND 46-656**

<b>Type of Correspondence.</b>	<b>Date</b>	<b>Contents</b>
<b>Original IND</b>	11/10/94	Submitted clinical study
<b>Annual Report</b>	2/21/96	As per 21 CFR 312.33
<b>Annual Report</b>	1/27/97	Study publication in Crit Care Med 1996:24:1793
<b>Annual Report</b>	3/27/98	As per 21 CFR 312.33
<b>Annual Report</b>	2/12/99	Clinical update on SOS
<b>Annual Report</b>	2/18/00	Submitted study of SOS
<b>Amendment</b>	4/12/00	Submitted information regarding SOS preparation
<b>Amendment</b>	1/31/01	Letter from University of Missouri to FDA indicating transfer of IND to Santarus
<b>Amendment</b>	2/2/01	Letter from Santarus to FDA acknowledging transfer
<b>Letter from FDA</b>	2/8/01	Letter from FDA acknowledging transfer of IND
<b>Phone Contact</b>	2/8/01	Conference with FDA regarding timing for subsequent discussions regarding clinical development program
<b>Amendment</b>	2/26/01	Letter to FDA regarding clinical studies and CMC information
<b>Phone Contact</b>	4/23/01	Phone call from FDA regarding ChocoBase
<b>Phone Contact</b>	4/26/01	Discussion regarding open-label study
<b>Letter from FDA</b>	6/14/01	Letter from FDA regarding the submission of IND Annual update
<b>Annual Report</b>	6/20/01	As per 21 CFR 213.33
<b>New Protocol</b>	7/6/01	Clinical Amendment: New study, OSB-IR-C01; Sensory

<b>Type of Correspondence.</b>	<b>Date</b>	<b>Contents</b>
<b>CMC Amendment</b>		benchmarking and excipient formulation development for OSB-IR CMC Amendment: DMF for API supplier
<b>Letter from FDA</b>	7/17/01	Letter from FDA denying request for a waiver of the 30 day waiting period
<b>CMC Amendment</b>	7/23/01	Santarus response to reviewer questions
<b>Amendment</b>	8/31/01	Pre-Phase 3 Meeting
<b>Fax from FDA</b>	9/14/01	Fax from FDA confirming the October 30th meeting
<b>Amendment</b>	11/8/01	Submission of Santarus October 30th pre-Phase 3 meeting minutes
<b>Letter from FDA</b>	11/19/01	Letter from FDA acknowledging receipt of change of address
<b>Clinical Amendment</b>	1/15/02	Draft Clinical Protocol and Questions
<b>Letter from FDA</b>	1/15/02	Receipt of FDA version of October 30, 2001 meeting minutes
<b>Clinical Amendment</b>	2/4/02	Additional clinical questions regarding C02 PK/PD study
<b>Phone Contact</b>	2/11/02	Request for teleconference with FDA regarding Phase 3 study questions
<b>Fax from FDA</b>	3/22/02	Fax from FDA documenting the Agency's response to meeting questions
<b>Letter from FDA</b>	3/25/02	Minutes of teleconference with FDA regarding questions about the C02 & C03 trials
<b>Clinical Amendment</b>	3/26/02	Sponsor response to issues from FDA March 25th 2002 teleconference
<b>CMC Amendment</b>	4/4/02	CMC update in support of Phase 3 study
<b>New Protocol</b>	4/5/02	New protocol: OSB-IR-C02; new PI
<b>Change in Protocol</b>	4/11/02	Protocol Amendment 1 - OSB-IR-C03: Transfer of sponsor responsibilities for C03 study
<b>Pediatric Study</b>	4/18/02	Proposed Pediatric Study Request: study summary for pediatric study OSB-IR-C04
<b>New Investigator</b>	5/1/02	New investigator for protocol OSB-IR-C02
<b>CMC Amendment</b>	5/10/02	Analytical test results and DMF authorization letter

<b>Type of Correspondence.</b>	<b>Date</b>	<b>Contents</b>
<b>New Investigators</b>	5/23/02	New Principal Investigators (PIs) for OSB-IR-C03
<b>Letter from FDA</b>	5/28/02	Letter from FDA requesting responses to four CMC questions
<b>Annual Report</b>	5/31/02	IND Annual Report
<b>Updated IB</b>	6/4/02	Updated IB
<b>New Protocol</b>	6/4/02	New protocol - OSB-IR-C05
<b>Change in Protocol</b>	6/14/02	Protocol Amendment 1 - OSB-IR-C02
<b>New Investigators</b>	7/3/02	New PIs for OSB-IR-C03
<b>Change in Protocol Clinical Amendment</b>	7/12/02	OSB-IR-C02 - Protocol Amendment 2 and Statistical Analysis Plan; Administrative Analysis Plan for Phase 3 Study OSB IR-C03
<b>Meeting Request</b>	7/24/02	Meeting request to discuss 505(b)(2) NDA based on PK/PD data
<b>Letter from FDA</b>	7/31/02	FDA issued a letter to Santarus requesting Santarus review the SAN-05 C03 protocol to determine whether it should be registered in the Clinical Trial Data Bank
<b>New Investigators</b>	8/1/02	New PIs for OSB-IR-C03
<b>Letter from FDA</b>	08/13/02	FDA issued a letter giving comments & recommendations referring to the IND and 3/26/02 and 4/18/02 Amendments
<b>CMC Amendment</b>	8/19/02	Response to June 2, 2002 FDA CMC questions
<b>New Investigators</b>	9/09/02	New PIs for OSB-IR-C03
<b>CMC Amendment</b>	09/13/02	Amendment for OSB-IR-C06, Phase 1
<b>New Protocol - C06</b>	09/18/02	New Protocol OSB-IR-C06
<b>Letter from FDA</b>	09/23/02	Receipt of FDA version of March 25, 2002 meeting minutes
<b>Letter from FDA</b>	10/10/02	Letter from the FDA: response to the Proposed Pediatric Study Request; study summary for pediatric study OSB-IR C04
<b>Feedback</b>	10/11/02	Pre-NDA Request for Feedback

<b>Type of Correspondence.</b>	<b>Date</b>	<b>Contents</b>
<b>Request</b>		
<b>Feedback Request</b>	11/15/02	Letter to the FDA: requesting a feedback on proposed trademarks for OSB-IR
<b>New Investigators</b>	12/03/02	New PIs for OSB-IR-C03
<b>Clinical Amendment</b>	12/11/02	Statistical Analysis Plan for Study OSB-IR-CO5 & OSB-IR C06
<b>Letter from FDA</b>	12/31/02	FDA issued a letter to Santarus requesting Santarus review the SAN-05 C06 new protocol to determine whether it should be registered in the Clinical Trial Data Bank
<b>Pre-NDA CMC Meeting Request</b>	01/24/03	Letter to the FDA requesting a CMC Type B meeting in March
<b>Pre-NDA CMC Additional. Data</b>	02/03/03	Letter to FDA giving additional PK/PD data requested at the January 27, 2003 meeting
<b>Fax to FDA</b>	02/04/03	Faxed a copy of the Letter to FDA giving additional PK/PD data sent 02/03/03 to the FDA
<b>New Investigator</b>	02/07/03	New PIs for OSB-IR-C03
<b>Pre-NDA CMC Meeting Background Package</b>	02/17/03	Pre-meeting background package in preparation for the March 20, 2003 pre-NDA CMC meeting regarding OSB-IR
<b>Fee Waiver Request</b>	03/07/03	Request for small business fee waiver
<b>Response to Fee Waiver Request</b>	03/07/03	FDA acknowledgment letter sent in response to the Small Business Waiver Santarus' Request
<b>US SBA Letter: Requirements for Size Determination</b>	03/10/03	US SBA (Small Business Administration): letter explaining the requirements for qualifying a small size business, including Application for Small Business Size Determination Form
<b>Fax from FDA Answers to Pre-NDA CMC Meeting</b>	03/18/03	FDA answers to the Pre-NDA CMC meeting
<b>Santarus answers to US SBA - Size Determination</b>	03/24/03	Santarus letter sent to US SBA re: Requirements for a small size business determination

<b>Type of Correspondence.</b>	<b>Date</b>	<b>Contents</b>
<b>FDA Fax: Feedback on Oct 11, 2002 &amp; Amendment</b>	03/26/03	FDA feedback about the IND submission, Pre NDA clinical feedback
<b>Letter from FDA</b>	03/26/03	FDA feedback about the IND submission, Pre NDA clinical feedback (received 03/28/03.)
<b>Letter from US SBA</b>	03/27/03	Additional information request for the NDA small business fee waiver
<b>Letter to US SBA</b>	03/28/03	Information requested for small business fee waiver sent to US Small Business Administration
<b>Request for Tele-conference with FDA</b>	04/03/03	Request for Teleconference with FDA following the answer from FDA 03/26/03
<b>US SBA Letter Acceptation of Small Business Status</b>	04/07/03	Letter indicating that Santarus was determined to be a small business
<b>Letter from FDA</b>	04/15/03	FDA minutes of the 20 Mar 03 CMC meeting (received by Santarus on 05/02/03).
<b>New Investigators</b>	04/22/03	Protocol Amendment: New investigators and subinvestigators for study OSB-IR-C03.
<b>Letter to HHS</b>	05/09/03	Registration of Drug Establishment and document with Receipt date returned to Santarus by HHS
<b>Background Package</b>	05/13/03	Background Package for June 10, 2003 meeting
<b>Letter from FDA: Labeler code No: 68012</b>	05/15/03	Letter from FDA: Labeler code No: 68012
<b>Amendment to Background Package</b>	05/23/03	Amendment to June 10 Premeeting Background Package
<b>Annual Report</b>	05/30/03	Annual report sent to FDA.
<b>Fax from FDA</b>	06/06/03	FDA answers to questions for June 10 meeting.
<b>FDA Letter: Answers to Questions Meet</b>	06/09/03	FDA letter: answers to questions for June 10 meeting
<b>New</b>	06/26/03	Clinical Amendment: New investigators for study OSB-IR

<b>Type of Correspondence.</b>	<b>Date</b>	<b>Contents</b>
<b>Investigators</b>		C03.
<b>FDA Letter: June 10 Meeting Minutes</b>	07/14/03	Letter from FDA: Official minutes of June 10 meeting
<b>Clinical Amendment</b>	07/22/03	Statistical Analysis Plan for OSB-IR-C03
<b>Request for CMC Information</b>	09/10/03	CMC request for information re: content and format, etc.
<b>Protocol Amendment New Investigator</b>	10/08/03	Clinical amendment: Protocol Amendment 1 for OSB-IR-C07 and new investigator
<b>New Investigator</b>	11/18/03	Clinical amendment: new investigators for OSB-IR-C07.
<b>Statistical Analysis Plan</b>	11/21/03	Clinical Amendment: Statistical Analysis Plan for OSB-IR C07.
<b>Letter from FDA CMC Response</b>	12/02/03	Response to CMC questions asked during 6/10/03 meeting
<b>Letter from FDA OSB-IR-C07 Protocol</b>	12/18/03	Response to the Clinical Trial Protocol OSB-IR-C07 submitted on 10/8/03
<b>Clinical Reports</b>	04/02/04	Clinical Amendment requesting Agency to refer to the NDA 21-636 for the Clinical Trials Reports of C02, C05 and C06
<b>Annual Report</b>	05/25/04	Annual Report including a new Investigator's Brochure

#### Regulatory Review Period Activities for NDA 21-636

<b>Type of Correspondence.</b>	<b>Date</b>	<b>Contents</b>
<b>Letter to FDA: Original NDA</b>	08/14/03	Original New Drug Application
<b>Letter to FDA: Extra desk copies</b>	08/18/03	3 extra desk copies of Module 1 sent to FDA
<b>Letter to FDA: Paper Review Copies</b>	09/09/03	3 copies of Module 2, 3 copies of Module 5 and 1 copy of Module 3 sent to FDA

<b>Type of Correspondence.</b>	<b>Date</b>	<b>Contents</b>
<b>Letter from FDA</b>	09/29/03	Letter stating the receipt of the application
<b>Patent Certification</b>	10/15/03	Certification letter of the patent notification to interested parties of our NDA filing
<b>Fax from FDA Filing Review Letter</b>	10/24/03	Fax from FDA acknowledging the filing review letter
<b>Letter to FDA</b>	11/07/03	Documentation of return receipts of notice of Paragraph IV patent certification, as per 21 CFR 314.52(e)
<b>Letter from FDA</b>	11/14/03	Letter from FDA – Filing Review – Sent 10-24-03
<b>Patent Information 003</b>	12/09/03	Patent information sent to FDA
<b>Safety Update</b>	01/07/04	120-Day Safety Update sent to FDA
<b>Response to FDA Filing Letter</b>	01/15/04	Response to FDA filing review letter
<b>Fax from FDA-CDR</b>	01/20/04	Letter from FDA CDER Electronic Document Room Staff regarding Amendment previously submitted
<b>E-mail to FDA</b>	01/29/04	E-mail to FDA concerning the trade name for OSB-IR 20 mg
<b>Fax from FDA</b>	02/09/04	FDA faxed the letter with Tradename and labeling comments
<b>FDA Letter</b>	02/16/04	FDA letter with Tradename and labeling comments
<b>DP Stability Update</b>	02/18/04	Letter to FDA with the Drug Product Stability and Specification Update
<b>Proposed Labeling</b>	02/24/03	Letter to FDA regarding Proposed Labeling Text sent on a CD
<b>FDA Letter</b>	03/01/04	Information Request Letter regarding the CMC section
<b>FDA Letter</b>	03/01/04	Recommendation for Labeling: organization of the Clinical Pharmacology
<b>Response to Disc Rev Letter</b>	03/02/04	Letter and CD-ROM sent to Doc Control Room with Santarus response to February 9, 2004 Discipline Review Letter
<b>Stability Update</b>	03/11/04	Letter to FDA: Stability update

<b>Type of Correspondence.</b>	<b>Date</b>	<b>Contents</b>
<b>FDA Fax</b>	03/18/04	Fax from FDA: CMC Discipline Review Letter
<b>Final Labeling</b>	03/22/04	Letter to FDA: Final Labeling
<b>FDA Letter</b>	03/22/04	Letter from FDA: CMC Discipline Review Letter
<b>Patent Information</b>	03/30/04	Letter to FDA: new patent information, Form 3542a
<b>CMC &amp; Labeling</b>	04/05/04	Letter to FDA: Complete Response to March 16, 2004 Discipline Review Letter, included CMC and Labeling sections
<b>Fax to FDA</b>	04/07/04	Fax sent to FDA: Complete Response to March 16, 2004 Discipline Review Letter, included only the CMC section
<b>Revised PI</b>	04/09/04	Letter to FDA: Revised Prescribing Information
<b>E-mail to FDA Labels</b>	04/14/04	E-mail to FDA with packet and carton labels
<b>Follow-up to 15 Apr 04 Teleconference</b>	04/19/04	Letter sent to FDA with the Follow-up to 15 April 04 CMC Teleconference
<b>Proposed Revisions to Labeling</b>	04/20/04	Letter to FDA with the Proposed Revisions to Labeling.
<b>Fax from FDA Labeling Comments</b>	04/22/04	Fax from FDA: Comments about the Labeling for the Teleconference that will be held with FDA on April 26, 2004
<b>E-mail from FDA</b>	04/26/04	Labeling: Word version of FDA revision of Prescribing Information after teleconference meeting on April 26, 2004
<b>Prescribing Info</b>	04/27/04	Letter to FDA: Prescribing Information – New draft incorporating comments made at April 26, 2004 Labeling Teleconference
<b>Revised Labeling</b>	05/13/04	Revised Labeling: revised packets and cartons labeling (color labels)
<b>E-mail from FDA</b>	05/14/04	Labeling: Word version of FDA revision of Prescribing Information response to prescribing information sent on 4/27/04
<b>Revised Labeling</b>	05/18/04	Revised Labeling: prescribing information in pdf and Word format, packets and labels in Word format

<b>Type of Correspondence.</b>	<b>Date</b>	<b>Contents</b>
<b>Letter from FDA</b>	05/20/04	Response to Amendment, dated March 2, 2004, Trade Name and labeling
<b>E-mail from FDA</b>	05/25/04	DMETS comments to sponsor regarding the Trade Name
<b>Briefing Package</b>	05/28/04	for June 7, 2004 meeting with FDA regarding Trade Name
<b>E-mail from FDA</b>	06/02/04	Requested a copy of amendment to paragraph IV certification
<b>Fax from FDA</b>	06/04/04	Responses to questions for the June 7, 2004 meeting
<b>Fax from FDA</b>	06/07/04	CDER Electronic Document Room Staff: request for resubmission of amendment submitted 5/28
<b>Background Info for June 7, 2004 Meeting</b>	06/07/04	Background information given to FDA including: PI dated May 18, 2004, PI dated June 04, 2004, Labels and PI of eight other drugs
<b>June 7, 2004 Agenda</b>	06/07/04	June 07, 2004 meeting FDA agenda
<b>E-mail from FDA</b>	06/10/04	FDA Final Label
<b>E-mail to FDA</b>	06/11/04	Final Label (Package Insert) for "Rapinex" with edits
<b>E-mail to FDA</b>	06/14/04	Carton and Trade Labels without the Trade Name "Rapinex"
<b>FDA Fax</b>	06/15/04	Approval Letter and Final Printed Labeling (FPL)
<b>FDA Approval Letter</b>	06/15/04	Approval Letter and Final Printed Labeling (FPL)

Section 12: Patent eligibility and the length of extension claimed.

U.S. Patent No. 6,489,346 is eligible for extension for 433 days since:

- (a) It claims (1) the approved human drug product Zegerid™, and (2) the use of the approved human drug product;
- (b) The term of said patent has never previously been extended;
- (c) This application is submitted by the owner of record of the patent, The Curators of the University of Missouri;
- (d) The product has been subject to regulatory review prior to the commercial marketing or use under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act;
- (e) The product received permission for commercial marketing or use on June 15, 2004, and the application has been submitted within 60 days from that date;
- (f) The permission for commercial marketing or use of the product is believed to be the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act under which the regulatory review period occurred;
- (g) The term of the patent has not expired prior to this date of application; and
- (h) No other patent term has been extended for the same regulatory review period for this product;
- (i) As shown in the Declaration of David C. Yeomans, Ph.D., attached herewith, both a synergy and a pharmacological interaction exists between omeprazole and sodium bicarbonate. As discussed above, according to the M.P.E.P., an approved drug product having two or more active ingredients which are shown to have a synergistic effect or a pharmacological interaction should be considered to have a single active ingredient made of the two active ingredients. The term “active ingredient” is defined in the M.P.E.P. (§ 2752, page 2700-31) to be “the ingredient in the drug product that becomes therapeutically active when administered.” Applicant submits that it is the combination of omeprazole and sodium bicarbonate that becomes therapeutically active for the approved uses of Zegerid™.

The original expiration date of the patent from which the patent term extension will run is July 16, 2016 (as limited by a terminal disclaimer based on U.S. Patent No. 5,840,737).

The length of extension claimed is 433 days and was calculated as follows:

A regulatory review period (per 37 C.F.R. § 1.775(c)) of 3518 days was calculated as the sum of:

- (1) the number of days from the filing of IND No. 46-656, November 10, 1994, to the filing date of the NDA, August 15, 2003, or 3214 days; and
- (2) the number of days from the filing date of the NDA, August 15, 2003, to the date of approval of the NDA, June 15, 2004, or 304 days.

The term of extension is generally determined under 37 C.F.R. § 1.775(d) by subtracting from the number of days determined to be the regulatory review period, the following:

- (i) The number of days in the regulatory review period which were on or before the date on which the patent issued, which in this case is 2943 days (from November 10, 1994 – December 3, 2002);
- (ii) The number of days in the regulatory review period in which it is determined that the marketing applicant did not act with diligence (zero); and
- (iii) One-half of the number of days remaining in the period defined by 37 C.F.R. § 1.775(c)(1) after that period is reduced in accordance with 37 C.F.R. §§ 1.775(d)(1)(i) and (ii).

Importantly, the date to which the patent may be extended cannot exceed the earlier of 14 years from the date of approval of the NDA, or for patents issued after September 24, 1984, five years from the original expiration date of the patent.

Assuming there is a determination that there are no periods in which the marketing applicant failed to act with due diligence, the calculation under 37 C.F.R. §§ 1.775(d)(1) is as follows:

- 3507            The regulatory review period is calculated as the period starting on November 10, 1994 [day 1] up to and including June 15, 2004 [day 3507];
- 2946           The period starting on November 10, 1994 [day 1] up to and including December 3, 2002 [day 2946];
- 0                No lack of due diligence is assumed;
- ½ (3202-2946)    0.5 x (the period beginning on November 10, 1994 [day 1] up to and including August 15, 2003 [day 3202] – the period beginning on November 10, 1994 up to and including December 3, 2002).

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This number of days does not exceed five years and the record clearly indicates that Applicants were diligent. Therefore, Missouri submits that the term of U.S. Patent No. 6,489,346 should be extended for 433 days, from July 16, 2016 to September 22, 2017.

Section 13: Duty of Disclosure.

The applicant hereby acknowledges the duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Section 14: Fees.

The prescribed fee of \$1,120.00 for receiving and acting upon the application for extension should be debited from Deposit Account No. 13-0019. If additional fees are required, authorization is made to charge such fees to Deposit Account No. 13-0019.

Section 15: Correspondence Address.

Inquiries and correspondence should be addressed to:

Joseph A. Mahoney, Esq.  
 Reg. No. 38,956  
 Mayer, Brown, Rowe & Maw LLP  
 P.O. Box 2828  
 Chicago, IL 60690  
 (312) 701-8979

Section 16: Copies.

The original and two (2) duplicate copies of this application are being submitted pursuant to 37 C.F.R. § 1.740(b) and it is hereby certified that the copies are identical to the original.

Section 17: Declaration.

The undersigned:

1. Is a patent attorney authorized to practice before the Patent and Trademark Office who has general authority from the owner of record of U.S. Patent No. 6,489,346 to act on behalf of the owner in patent matters;
2. Has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.740;
3. Believes U.S. Patent No. 6,489,346 is subject to extension pursuant to 37 C.F.R. § 1.710 and 35 U.S.C. § 156;
4. Believes an extension for 433 days, the length claimed, is justified under 35 U.S.C. § 156 and the applicable regulations; and
5. Believes the patent for which the extension is being sought meets the conditions for extension of the term of the patent as set forth in 37 C.F.R. § 1.720.

Any questions concerning this application may be directed to the below noted attorney.

Respectfully submitted,

By: Mayer, Brown, Rowe & Maw LLP

By: 

Joseph A. Mahoney, Reg. No. 38,956

**CUSTOMER NUMBER 26565**  
**MAYER, BROWN, ROWE & MAW LLP**  
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Chicago, IL 60690-2828  
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Facsimile: (312) 706-9000

**Enclosures:**

Attachment 1: FDA Approval Letter.

Attachment 2: U.S. Patent No. 6,489,346.

Attachment 3: Maintenance Fee schedule in respect of U.S. Patent No. 6,489,346.

Attachment 4: Terminal Disclaimer filed in respect of U.S. Patent No. 6,489,346.

Attachment 5: Two Certificates of Correction filed in respect of U.S. Patent No. 6,489,346.

Attachment 6: Declaration of Dr. David C. Yeomans (including Exhibits A – H).