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April 17, 2006

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VIA FEDERAL EXPRESS

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Attn: Glenn M. Engelmann
Vice President Policy, Legal and
Scientific Affairs, General Counsel
Attn: Judy W. Firor
Regulatory Affairs

Re: **Omeprazole Delayed Release Tablets, 20 mg**
Our reference: 236869

To Whom It May Concern:

We are writing on behalf of Dexcel Pharma Technologies Ltd. ("Dexcel"), pursuant to 21 U.S.C. § 355(b)(3)(C)(i) and (ii), to inform you that Dexcel, in order to obtain approval to engage in the commercial manufacture, use or sale of 20 mg delayed release omeprazole tablets, for over-the-counter sale ("Dexcel's Tablets"), submitted to the United States Food and Drug Administration ("FDA") a New Drug Application ("Dexcel's NDA"), under 21 U.S.C. § 355(b)(1)(A-G) and (b)(2)(A), and which has been assigned NDA No. 22-032 ("Dexcel's NDA"). Dexcel's NDA identifies 20 mg tablets of PRILOSEC® OTC (omeprazole magnesium

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delayed release tablets), approved under NDA No. 021229, and PRILOSEC® 10 mg, 20 mg, and 40 mg capsules (omeprazole delayed release pellets), approved under NDA No. 019810, both of which are the Listed Drugs referenced in the Orange Book for their respective NDAs.

Dexcel's NDA includes a certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) with respect to U.S. Patent Nos. 4,786,505 ("the '505 patent") and 4,853,230 ("the '230 patent"), both of which have an original expiration date of April 20, 2007, and have been granted pediatric exclusivity extensions as indicated in the Orange Book. Dexcel has certified that, in Dexcel's opinion, said patents are invalid, unenforceable, and/or not infringed by Dexcel's Tablets. Dexcel intends to market its Tablets before the pediatric extension expiration date of the '505 and '230 patents.

We are writing to Aktiebolaget Hassle, Molndal, Sweden, a Corporation of Sweden ("Aktiebolaget Hassle"), as, upon information and belief, the current owner of the '505 and '230 patents, and to AstraZeneca, as the entity listed with the FDA as the current holder of NDA Nos. 021229 and 019810. This letter represents notice to Aktiebolaget Hassle and AstraZeneca of its contents. As required by 21 U.S.C. § 355(b)(3)(B)(i), a detailed statement of the factual and legal basis upon which Dexcel bases its opinion regarding the '505 and '230 patents is set forth below.

Pursuant to 21 C.F.R. § 314.95(e), Dexcel requested and received permission from the FDA to send this notice by means other than registered or certified mail. Specifically, Dexcel requested that it be allowed to send this notice by Federal Express® courier. The FDA granted Dexcel's request prior to this notice being sent.

I. APPLICABLE LEGAL STANDARDS

There are generally two ways a claim can be directly infringed. A claim can be either (a) literally infringed or (b) infringed under what is known as the "doctrine of equivalents." In order to determine whether a product or process infringes a U.S. patent, the courts apply a two-step test for each invention claimed. First, the court construes or interprets the claim and resolves any dispute as to the meaning of the particular claimed technology. The patented invention, as set forth in the words of the patent claims, must be clearly understood. This is a question of claim interpretation, which is determined by the court as a matter of law. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 116 S.Ct. 1384, 134 LEd.2d 577 (1996) (en banc), aff'd, 517 U.S. 370, 116 S.Ct.1384, 38 U.S.P.Q.2d 1461 (1996). Next, under the second step of the analysis, the properly construed claim is compared to the accused product to determine whether there is literal infringement or a claim of infringement under the doctrine of equivalents. *Mas-Hamilton Group v. La Gard, Inc.*, 156 F.3d 1206, 1211-12, 48 U.S.P.Q.2d 1010, 1014-15 (Fed.Cir. 1998). If the accused product has every element of a claim, literal infringement is established. *Acco Brands, Inc. v. Micro Sec. Devices, Inc.*, 346 F.3d 1075, 1081 (Fed. Cir. 2003); *Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997). All claim elements are material and must be present to find infringement. *Odetics, Inc. v. Storage Tech. Corp.*, 185 F.3d 1259, 1268. ("It is of course axiomatic that '[e]ach element contained in a patent claim is deemed material to determining the scope of the patented invention.'" (quoting *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997))).

If there is not a literal correspondence between the elements of a claim and the accused product, there may still be infringement under the doctrine of equivalents if the accused product contains the substantial equivalent of each and every one of the elements of the asserted claim. *Eagle Comtronics, Inc. v. Arrow Communication Labs.*, 305 F.3d 1303, 1316 (Fed. Cir. 2002); *Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1349 (Fed. Cir. 1998). This doctrine comes into play only when literal infringement is not present. Under the doctrine of equivalents, an accused product that does not literally infringe a claim may be found to infringe if it performs substantially the same function in substantially the same way to obtain the same or substantially the same result as the claimed invention. *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1349 (Fed. Cir. 2001). Importantly, even under the doctrine of equivalents, every claim element or its equivalent must be present in the accused device. *Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1333 (Fed. Cir. 2001). "No claimed element, or an equivalent thereof, can be absent if the doctrine of equivalents is invoked." *Id.*

II. THE '505 AND '230 PATENTS

The '505 patent

The '505 patent contains two independent claims, claims 1 and 14. Claim 1 specifies an oral pharmaceutical preparation comprising (a) a core region comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone; (b) an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of materials selected from among tablet excipients and polymeric film-forming compounds; and (c) an outer layer disposed on said subcoating comprising an enteric coating.

Claim 14 specifies a process for preparing an oral pharmaceutical preparation as recited in Claim 1.

The '230 patent

The '230 patent contains two independent claims, claims 1 and 12. Claim 1 specifies a pharmaceutical preparation containing (a) an alkaline reacting core comprising an acid-labile pharmaceutically active substance and an alkaline reacting compound different from said active substance, an alkaline salt of an acid labile pharmaceutically active substance and an alkaline reacting compound different from said active substances; (b) an inert subcoating which rapidly dissolves or disintegrates in water disposed on said core region, said subcoating comprising one or more layers comprising materials selected from the group consisting of tablet excipients, film-forming compounds and alkaline compounds; and (c) an enteric coating layer surrounding said subcoating layer, wherein the subcoating layer isolates the alkaline reacting core from the enteric coating layer such that the stability of the preparation is enhanced.

Claim 12 specifies a process for preparing an oral pharmaceutical preparation as recited in Claim 1.

III. ANALYSIS

All of the independent claims of the '505 patent and the '230 patent require the presence of "an inert subcoating" or "one or more inert reacting subcoating layers." Although the claims use varying terminology to identify the region between the "core" or "core region" and the "enteric coating" or "enteric coating layer", any intended differences are irrelevant. The claims affirmatively require that the presence of an inert subcoating layer between the surface of the core and the enteric coating and, accordingly, the terms "an inert subcoating", "one or more inert reacting subcoating layers" and "a separating layer" all identify the same inert subcoating layer and are used interchangeably.

Dexcel's omeprazole tablets differ from the inventions claimed in the '505 patent and the '230 patent in several particulars. Dexcel's Tablets are manufactured using conventional processing steps. The active ingredient, omeprazole, and other excipients are mixed together, compressed into tablets and then coated with an enteric coating. There is no step involving the application or formation of a subcoating or separating layer between the core and the enteric coating. Based on the aforementioned manufacturing procedure used by Dexcel to make its own omeprazole tablets there is no infringement of any of the claims of the '505 and '230 patents.

As all independent claims of the '505 and '230 patents require the presence of a subcoating or separating layer between core and the enteric coating and no such subcoating or separating layer is present in Dexcel's omeprazole tablets, there is no literal infringement of any of the claims of those patents.

Further, there is no structure in the Dexcel omeprazole tablets that could provide the basis for arguing infringement under the doctrine of equivalents. There simply is nothing in the Dexcel omeprazole tablets that performs the same function as a subcoating or separating layer, in substantially the same way to achieve substantially the same result. Indeed, no equivalent of such a claim element is present. Accordingly, there can be no infringement under the doctrine of equivalents.

IV. JURISDICTION

Dexcel hereby consents to jurisdiction in the United States District Court for the Eastern District of Virginia, Norfolk Division, solely for purposes of any infringement action based upon its aforementioned NDA. Dexcel maintains an office located at Wainwright Building, 229 West Bute Street, Suite 407, Norfolk, Virginia 23510.

V. CONCLUSION

For the reasons set forth above, Dexcel's Tablets do not infringe any of the claims of the '505 and '230 patents.

To the extent that process claims are discussed above, any such discussion is for informational purposes only. As process claims cannot be listed in the Orange Book, no certification or detailed statement regarding them is required and such claims cannot form the basis of any 30 month statutory prohibition against approval of Dexcel's NDA.

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Pursuant to 21 U.S.C. § 355(c)(3)(D)(i)(III), Dexcel hereby extends Aktiebolaget Hassle and AstraZeneca an Offer of Confidential Access to Dexcel's NDA pursuant to a mutually agreeable confidentiality agreement that contains reasonable restrictions as to persons entitled to access and on the use and disposition of any information accessed.

Please be advised that Dexcel intends to obtain final approval of its NDA and proceed to market its Tablets as soon as permitted by applicable statutes and regulations.

Dexcel expressly reserves the right to challenge the validity and enforceability of the '505 and '230 patents and/or any assertion of infringement that AstraZeneca, Aktiebolaget Hassle and/or the current owner of the '505 and '230 patents might make on new, other, or further grounds should such grounds become apparent during any ensuing litigation between the parties.

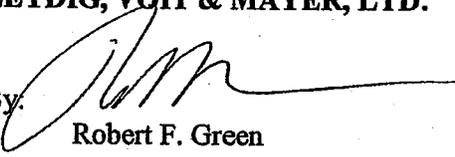
As Aktiebolaget Hassle and AstraZeneca are surely aware, institution of baseless litigation against an applicant seeking approval to market a generic drug product can give rise to antitrust liability. The Federal Trade Commission ("FTC") has in the past strongly condemned such tactics. Suffice it to say, should Aktiebolaget Hassle or AstraZeneca choose the precarious route of filing suit against Dexcel, it is reasonably certain that the FTC will have a great interest in such litigation.

So there is no misunderstanding, Dexcel will not only aggressively defend against any baseless lawsuit filed by Aktiebolaget Hassle or AstraZeneca, Dexcel also will seek all appropriate remedies to redress what could only be viewed as a fraudulent misuse of the '505 and '230 patents, which would harm not only Dexcel but the patients who take Prilosec® OTC tablets, resulting in antitrust liability for Aktiebolaget Hassle and AstraZeneca.

If you have any questions after reviewing this letter, please feel free to contact us to discuss this matter.

Very truly yours,

LEYDIG, VOIT & MAYER, LTD.

By: 

Robert F. Green

RFG/SSM/krs

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VIA FEDERAL EXPRESS

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Attn: Judy W. Firor
Regulatory Affairs

Re: **Omeprazole Delayed Release Tablets, 20 mg**
Our reference: 236869

To Whom It May Concern:

We are writing on behalf of Dexcel Pharma Technologies Ltd. ("Dexcel"), pursuant to 21 U.S.C. § 355(b)(3)(C)(i) and (ii), to inform you that Dexcel, in order to obtain approval to engage in the commercial manufacture, use or sale of 20 mg delayed release omeprazole tablets for over-the-counter sale ("Dexcel's Tablets"), submitted to the United States Food and Drug Administration ("FDA") a New Drug Application ("Dexcel's NDA"), under 21 U.S.C. § 355(b)(1)(A-G) and (b)(2)(A), and which has been assigned NDA No. 22-032 ("Dexcel's NDA"). Dexcel's NDA identifies 20 mg tablets of PRILOSEC® OTC (omeprazole magnesium delayed release tablets), approved under NDA No. 021229, and PRILOSEC® 10 mg, 20 mg, and 40 mg capsules (omeprazole delayed release pellets), approved under NDA No. 019810, both of which are the Listed Drugs referenced in the Orange Book for their respective NDAs.

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Dexcel's NDA includes a certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) with respect to U.S. Patent Nos. 6,147,103 ("the '103 patent"), 6,166,213 ("the '213 patent"), and 6,191,148 ("the '148 patent"), all of which expire on October 9, 2018, and have been granted pediatric exclusivity. Dexcel has certified that, in Dexcel's opinion, said patents are invalid, unenforceable, and/or not infringed by Dexcel's Tablets. Dexcel intends to market its Tablets before the expiration date of the pediatric exclusivity period for the '103, '213 and '148 patents.

We are writing to Merck & Co., Inc. ("Merck"), as, upon information and belief, the current owner of the '103, '213 and '148 patents, and to AstraZeneca, as the entity listed with the FDA as the current holder of NDA Nos. 021229 and 019810. This letter represents notice to Merck and AstraZeneca of its contents. As required by 21 U.S.C. § 355(b)(3)(B)(i), a detailed statement of the factual and legal basis upon which Dexcel bases its opinion regarding the '103, '213 and '148 patents is set forth below.

Pursuant to 21 C.F.R. § 314.95(e), Dexcel requested and received permission from the FDA to send this notice by means other than registered or certified mail. Specifically, Dexcel requested that it be allowed to send this notice by Federal Express® courier. The FDA granted Dexcel's request prior to this notice being sent.

I. APPLICABLE LEGAL STANDARDS

A. The Law with Respect to Infringement

There are generally two ways a claim can be directly infringed. A claim can be either (a) literally infringed or (b) infringed under what is known as the "doctrine of equivalents." In order to determine whether a product or process infringes a U.S. patent, the courts apply a two-step test for each invention claimed. First, the court construes or interprets the claim and resolves any dispute as to the meaning of the particular claimed technology. The patented invention, as set forth in the words of the patent claims, must be clearly understood. This is a question of claim interpretation, which is determined by the court as a matter of law. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996) (en banc), aff'd, 517 U.S. 370, 116 S.Ct. 1384, 38 U.S.P.Q.2d 1461 (1996). Next, under the second step of the analysis, the properly construed claim is compared to the accused product to determine whether there is literal infringement or a claim of infringement under the doctrine of equivalents. *Mas-Hamilton Group v. La Gard, Inc.*, 156 F.3d 1206, 1211-12, 48 U.S.P.Q.2d 1010, 1014-15 (Fed.Cir. 1998). If the accused product has every element of a claim, literal infringement is established. *Acco Brands, Inc. v. Micro Sec. Devices, Inc.*, 346 F.3d 1075, 1081 (Fed. Cir. 2003); *Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997). All claim elements are material and must be present to find infringement. *Odetics, Inc. v. Storage Tech. Corp.*, 185 F.3d 1259, 1268. ("It is of course axiomatic that [e]ach element contained in a patent claim is deemed material to determining the scope of the patented invention." (quoting *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997))).

If there is not a literal correspondence between the elements of a claim and the accused product, there may still be infringement under the doctrine of equivalents if the accused product contains the substantial equivalent of each and every one of the elements of the asserted claim. *Eagle Comtronics, Inc. v. Arrow Communication Labs.*, 305 F.3d 1303, 1316 (Fed. Cir. 2002);

Digital Biometrics, Inc. v. Identix, Inc., 149 F.3d 1335, 1349 (Fed. Cir. 1998). This doctrine comes into play only when literal infringement is not present. Under the doctrine of equivalents, an accused product that does not literally infringe a claim may be found to infringe if it performs substantially the same function in substantially the same way to obtain the same or substantially the same result as the claimed invention. *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1349 (Fed. Cir. 2001). Importantly, even under the doctrine of equivalents, every claim element or its equivalent must be present in the accused device. *Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1333 (Fed. Cir. 2001). "No claimed element, or an equivalent thereof, can be absent if the doctrine of equivalents is invoked." *Id.*

Under the doctrine of "prosecution history estoppel," a patent holder is presumed to have surrendered all equivalents of a claim element under the doctrine of equivalents if, during the course of prosecution, either voluntarily or involuntarily, a narrowing amendment is made to the claim element to satisfy any requirement of the Patent Act. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 122 S.Ct. 1831, 1838-39 (2002).

B. The Law with Respect to Invalidity

Patents may be held invalid for lack of patentable subject matter, lack of novelty and various statutory bars, obviousness, and deficiencies in the specification disclosure and the claims. 35 U.S.C. §§ 101-103, 112 (2004).

1. Prior Art - Anticipation

Validity is often challenged based on the prior art. A patent claim is invalid because of "anticipation" when a single prior art reference contains each and every limitation, or element, of the claim. 35 U.S.C. § 102 (2004); *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 545 (Fed. Cir. 1998); *Union Oil*, 208 F.3d at 995. The prior art reference must describe the patent claim with sufficient clarity and detail to establish that the invention existed. *ATD Corp.*, 159 F.3d at 545. However, the prior art reference may anticipate without explicitly disclosing a limitation if that limitation was necessarily present, or inherent, in the prior art reference. Furthermore, a prior art reference can disclose enough for inherent anticipation even if the inherent teaching was unappreciated by those of ordinary skill at the time. *Toro Co. v. Deere & Co.*, 69 U.S.P.Q.2d 1584, 1589-90 (Fed. Cir. 2004). Thus, the doctrine of inherency protects the public's practice of the prior art even if they did not understand the principles that allow it to operate. *Schering Corp. v. Geneva Pharm., Inc.*, 399 F.3d 1373, 1377-80 (Fed. Cir. 2003).

2. The On Sale Bar Under § 102(b)

A patent is invalid under section 102(b) if "the invention was . . . on sale in this country, more than one year prior to the date of the application for patent in the United States . . .", which is known as the critical date. Before the critical date, the invention must both be the subject of a commercial sale or offer for sale and be "ready for patenting." See *Pfaff v. Wells Electronics Inc.* 48 U.S.P.Q.2d 1641, 1646-47 (Fed. Cir. 2005). Furthermore, the statutory on-sale bar is not subject to exceptions for sales made by third parties either innocently or fraudulently. See *Evans Cooling Sys., Inc. v. General Motors Corp.*, 125 F.3d 1448, 1453-54, 44 U.S.P.Q.3d 1037, 1040-42 (Fed. Cir. 1997).

3. Public Use Under § 102(b)

“Public use [under 35 U.S.C. § 102(b)] includes any use of the claimed invention by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor.” *Netscape Communications Corp. v. Konrad*, 295 F.3d 1315, 1320 [63 U.S.P.Q.2d 1580] (Fed. Cir. 2002).

4. Obviousness - 35 U.S.C. § 103

A patent claim is invalid if, at the time the invention was made, the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. 35 U.S.C. § 103(a); *see also Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

II. THE '103, '213 AND '148 PATENTS

The '103 patent

The '103 patent contains a total of 8 claims with four independent claims, claim 1, 2, 5 and 6. Claim 1 specifies a composition comprising 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) having less than three parts per million of residual aromatic hydrocarbon solvent and 10-20 p.p.m. of residual methanol relative to omeprazole.

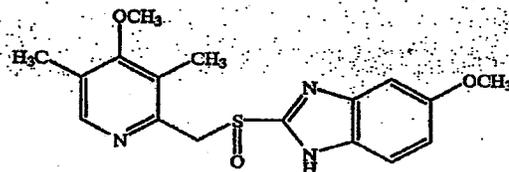
Claim 2 differs from Claim 1 in that it requires a “chlorinated aliphatic hydrocarbon” rather than the “aromatic hydrocarbon” of Claim 1.

Claim 5 differs from Claim 1 only in that it additionally requires “a pharmaceutically acceptable excipient”.

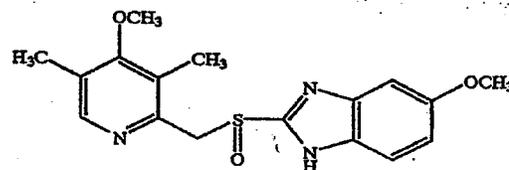
Claim 6 differs from Claim 2 only in that it additionally requires “a pharmaceutically acceptable excipient”.

The '213 patent

The '213 patent contains a total of 29 claims with 3 independent claims, claims 1, 26 and 27. Claim 1 specifies a process for the preparation of omeprazole, having the formula I,



which comprises (a) treating, at about -5 to $+5^\circ\text{C}$., a buffered solution of pyrimetazole, having the formula II, in a non-alcoholic organic



reaction solvent, with one equivalent, relative to the number of moles of said pyrimetazole, of meta-chloroperoxybenzoic [acid] dissolved in the non-alcoholic organic reaction solvent in admixture with an alcoholic presence of an aqueous base; (b) separating the aqueous phase of the aged reaction mixture from the organic phase; and (c) removing residual non-alcoholic organic reaction solvent from said aqueous phase followed by re-adjusting the alcoholic solvent concentration to about 15% v/v.

Claim 26 specifies 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) containing less than three parts per million of residual aromatic hydrocarbon solvent and 10-20 p.p.m. of residual methanol.

Claim 27 differs from Claim 26 in that it requires a "chlorinated aliphatic hydrocarbon" rather than the "aromatic hydrocarbon" of Claim 26.

The '148 patent

The '148 patent contains a total of 16 claims with one independent claim. Claim 1 specifies 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole (omeprazole) of greater than 99.94% purity as determined by high-performance liquid chromatography and having less than 500 parts per million (p.p.m.) of residual ethanol relative to omeprazole.

III. ANALYSIS

A. Invalidity

Dexcel has obtained evidence related to a sale and shipment of omeprazole by its API supplier in March 1997. The sale, and hence any "offer for sale" of the omeprazole, occurred more than one year prior to the earliest possible filing date of any application upon which the '148 patent is based. If Merck argues that the omeprazole in Dexcel's Tablets infringes the claims of the '148 patent either literally or under the doctrine of equivalents, then the prior sale anticipates claims 1-4, 6-7 and 9 of the '148 patent.

Claim 11 relates to any composition containing omeprazole of claim 1 and claim 14 relates to the omeprazole of claim 1 in a pharmaceutical formulation. At the time the application resulting in the '148 patent was filed, it was known in the art that omeprazole could be made into finished dosage forms that could be used to treat gastrointestinal disorders. *See*, U.S. Patent No. 4,786,505. Accordingly, claims 11 and 14 should be found to be invalid under 35 U.S.C. § 103 if Merck now argues that they are infringed by the use of the omeprazole as described above to make Dexcel's Tablets.

B. Non-infringement

The three independent claims of the '103 patent all require that the claimed omeprazole contain "10-20 p.p.m. of residual methanol." Dexcel has limited the quantity of methanol in the API that will be used to make Dexcel's Tablets to be below 10 or above 20 p.p.m. Accordingly there is no literal infringement of any claim of the '103 patent and as the claimed range was urged to distinguish over the prior art it should not be accorded any degree of equivalence under the doctrine of equivalents.

Claims 1-21 of the '213 patent are all process claims that require that omeprazole be made by oxidizing pyrimetazole, *inter alia*, wherein the oxidizing agent is meta-chloroperoxybenzoic acid used at a specific ratio of one equivalent of acid to one mole of pyrimetazole. The use of this specific oxidizing agent at such a specific ratio was argued by the applicants to be critical. The omeprazole in Dexcel's Tablets is not made by a process using meta-chloroperoxybenzoic acid, and thus, Dexcel does not infringe any of claims 1-21.

Claims 22-25 of the '213 patent are all nominally "composition" claims that depend directly or indirectly upon the process claims 1-21, and ultimately each of claims 22-25 depends indirectly upon claim 1. Construing the language "obtained by the process of" as a limitation that requires that the claimed product be manufactured by the claimed process, the omeprazole in Dexcel's Tablets does not infringe claims 22-25 for the reasons stated above.

Each of claims 26-29 of the '213 patent encompasses omeprazole that must contain 10-20 p.p.m. of residual methanol. As explained previously with respect to the '103 patent, Dexcel has limited the quantity of methanol in the API used to make its Tablets to be below 10 or above 20 p.p.m. Therefore, the omeprazole in Dexcel's Tablets does not infringe any of claims 26-29 either literally or under the doctrine of equivalents.

Claim 1 of the '148 patent is directed to a product claim that characterizes omeprazole based upon two parameters, purity and "residual ethanol". The proper construction of Claim 1 requires that the term "residual ethanol" means ethanol that remains from its use in the synthesis of the omeprazole and that the term "omeprazole" means omeprazole that is made using ethanol at some point in its synthesis.

The Court of Appeals for the Federal Circuit recently addressed this claim construction issue in *3M Innovative Proprs. Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 69 U.S.P.Q.2d 1050 (Fed. Cir. 2003). In that case the Court of Appeals recognized that although product claims are not usually limited by non-recited process limitations, to determine if such process of manufacture limitations should be read into the claims one must review the intrinsic evidence.

The '148 patent describes the product of the invention as containing "diminished levels of alcoholic solvent." "Omeprazole and compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and diminished levels of alcoholic solvent are also disclosed." (Col. 1, lines 16-19) Telling is the fact that the alcohol is referenced as "alcoholic solvent". The patent explains that the prior art omeprazole presented quality problems due to the "occlusion of residual solvents" during crystallization.

Accordingly, the proper construction of claim 1 requires that the term "residual ethanol" means ethanol that remains from its use in the synthesis of the omeprazole and the term "omeprazole" means omeprazole that is made using ethanol at some point in its synthesis.

No ethanol is used at any point in the manufacture or crystallization of the omeprazole used in Dexcel's Tablets. Accordingly, there can be no infringement of claim 1 of the '148 patent. Further, as all remaining claims depend directly or indirectly from claim 1, they too cannot be infringed.

IV. JURISDICTION

Dexcel hereby consents to jurisdiction in the United States District Court for the Eastern District of Virginia, Norfolk Division, solely for purposes of any infringement action based upon its aforementioned NDA. Dexcel maintains an office located at Wainwright Building, 229 West Bute Street, Suite 407, Norfolk, Virginia 23510.

V. CONCLUSION

For the reasons set forth above, Dexcel's Tablets do not infringe any of the claims of the '103, '213 and '148 patents and claims 1-4, 6-7, 9, 11 and 14 of the '148 patent if construed to be infringed, are invalid.

To the extent that process claims are discussed above, any such discussion is for informational purposes only. As process claims cannot be listed in the Orange Book, no certification or detailed statement regarding them is required and such claims cannot form the basis of any 30 month statutory prohibition against approval of Dexcel's NDA.

April 17, 2006

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Pursuant to 21 U.S.C. § 355(c)(3)(D)(i)(III), Dexcel hereby extends Merck and AstraZeneca an Offer of Confidential Access to Dexcel's NDA pursuant to a mutually agreeable confidentiality agreement that contains reasonable restrictions as to persons entitled to access and on the use and disposition of any information accessed.

Please be advised that Dexcel intends to obtain final approval of its NDA and proceed to market its Tablets as soon as permitted by applicable statutes and regulations.

Dexcel expressly reserves the right to challenge the validity and enforceability of the '103, '213 and '148 patents and/or any assertion of infringement that AstraZeneca, Merck and/or the current owner of the '103, '213 and '148 patents might make on new, other, or further grounds should such grounds become apparent during any ensuing litigation between the parties.

As Merck and AstraZeneca are surely aware, institution of baseless litigation against an applicant seeking approval to market a generic drug product can give rise to antitrust liability. The Federal Trade Commission ("FTC") has in the past strongly condemned such tactics. Suffice it to say, should Merck or AstraZeneca choose the precarious route of filing suit against Dexcel, it is reasonably certain that the FTC will have a great interest in such litigation.

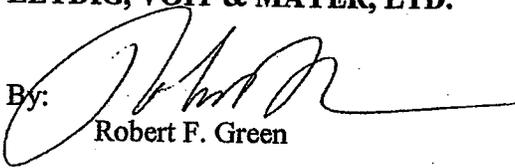
So there is no misunderstanding, Dexcel will not only aggressively defend against any baseless lawsuit filed by Merck or AstraZeneca, Dexcel also will seek all appropriate remedies to redress what could only be viewed as a fraudulent misuse of the '103, '213 and '148 patents, which would harm not only Dexcel but the patients who take Prilosec® OTC tablets, resulting in antitrust liability for Merck and AstraZeneca.

If you have any questions after reviewing this letter, please feel free to contact us to discuss this matter.

Very truly yours,

LEYDIG, VOIT & MAYER, LTD.

By:


Robert F. Green

RFG/SSM/krs

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May 4, 2006

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1155 Avenue of the Americas
New York, NY 10036

Re: **Omeprazole Delayed Release Tablets, 20 mg**
Our reference: 236869

To Whom It May Concern:

We are writing on behalf of Dexcel Pharma Technologies Ltd. ("Dexcel"), pursuant to 21 U.S.C. § 355(b)(3)(C)(i) and (ii), to inform you that Dexcel, in order to obtain approval to engage in the commercial manufacture, use or sale of 20 mg delayed release omeprazole tablets, for over-the-counter sale ("Dexcel's Tablets"), submitted to the United States Food and Drug Administration ("FDA") a New Drug Application ("Dexcel's NDA"), under 21 U.S.C. § 355(b)(1)(A-G) and (b)(2)(A), and which has been assigned NDA No. 22-032 ("Dexcel's NDA"). Dexcel's NDA identifies 20 mg tablets of PRILOSEC® OTC (omeprazole magnesium delayed release tablets), approved under NDA No. 021229, and PRILOSEC® 10 mg, 20 mg, and 40 mg capsules (omeprazole delayed release pellets), approved under NDA No. 019810, both of which are the Listed Drugs referenced in the Orange Book for their respective NDAs.

Dexcel's NDA includes a certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) with respect to U.S. Patent Nos. 4,786,505 ("the '505 patent") and 4,853,230 ("the '230 patent"), both

exclusivity extensions as indicated in the Orange Book. Dexcel has certified that, in Dexcel's opinion, said patents are invalid, unenforceable, and/or not infringed by Dexcel's Tablets. Dexcel intends to market its Tablets before the pediatric extension expiration date of the '505 and '230 patents.

We are writing to Aktiebolaget Hassle, Molndal, Sweden, a Corporation of Sweden ("Aktiebolaget Hassle"), as, upon information and belief, the current owner of the '505 and '230 patents, and to AstraZeneca, as the entity listed with the FDA as the current holder of NDA Nos. 021229 and 019810. This letter represents notice to Aktiebolaget Hassle and AstraZeneca of its contents. As required by 21 U.S.C. § 355(b)(3)(B)(i), a detailed statement of the factual and legal basis upon which Dexcel bases its opinion regarding the '505 and '230 patents is set forth below.

Pursuant to 21 C.F.R. § 314.95(e), Dexcel requested and received permission from the FDA to send this notice by means other than registered or certified mail. Specifically, Dexcel requested that it be allowed to send this notice by Federal Express® courier. The FDA granted Dexcel's request prior to this notice being sent.

I. APPLICABLE LEGAL STANDARDS

There are generally two ways a claim can be directly infringed. A claim can be either (a) literally infringed or (b) infringed under what is known as the "doctrine of equivalents." In order to determine whether a product or process infringes a U.S. patent, the courts apply a two-step test for each invention claimed. First, the court construes or interprets the claim and resolves any dispute as to the meaning of the particular claimed technology. The patented invention, as set forth in the words of the patent claims, must be clearly understood. This is a question of claim interpretation, which is determined by the court as a matter of law. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 116 S.Ct. 1384, 134 LEd.2d 577 (1996) (en banc), aff'd, 517 U.S. 370, 116 S.Ct.1384, 38 U.S.P.Q.2d 1461 (1996). Next, under the second step of the analysis, the properly construed claim is compared to the accused product to determine whether there is literal infringement or a claim of infringement under the doctrine of equivalents. *Mas-Hamilton Group v. La Gard, Inc.*, 156 F.3d 1206, 1211-12, 48 U.S.P.Q.2d 1010, 1014-15 (Fed.Cir. 1998). If the accused product has every element of a claim, literal infringement is established. *Acco Brands, Inc. v. Micro Sec. Devices, Inc.*, 346 F.3d 1075, 1081 (Fed. Cir. 2003); *Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997). All claim elements are material and must be present to find infringement. *Odetics, Inc. v. Storage Tech. Corp.*, 185 F.3d 1259, 1268. ("It is of course axiomatic that '[e]ach element contained in a patent claim is deemed material to determining the scope of the patented invention.'" (quoting *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997))).

If there is not a literal correspondence between the elements of a claim and the accused product, there may still be infringement under the doctrine of equivalents if the accused product contains the substantial equivalent of each and every one of the elements of the asserted claim. *Eagle Comtronics, Inc. v. Arrow Communication Labs.*, 305 F.3d 1303, 1316 (Fed. Cir. 2002); *Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1349 (Fed. Cir. 1998). This doctrine comes into play only when literal infringement is not present. Under the doctrine of equivalents, an accused product that does not literally infringe a claim may be found to infringe if it performs

substantially the same function in substantially the same way to obtain the same or substantially the same result as the claimed invention. *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1349 (Fed. Cir. 2001). Importantly, even under the doctrine of equivalents, every claim element or its equivalent must be present in the accused device. *Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1333 (Fed. Cir. 2001). "No claimed element, or an equivalent thereof, can be absent if the doctrine of equivalents is invoked." *Id.*

II. THE '505 AND '230 PATENTS

The '505 patent

The '505 patent contains two independent claims, claims 1 and 14. Claim 1 specifies an oral pharmaceutical preparation comprising (a) a core region comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone; (b) an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of materials selected from among tablet excipients and polymeric film-forming compounds; and (c) an outer layer disposed on said subcoating comprising an enteric coating.

Claim 14 specifies a process for preparing an oral pharmaceutical preparation as recited in Claim 1.

The '230 patent

The '230 patent contains two independent claims, claims 1 and 12. Claim 1 specifies a pharmaceutical preparation containing (a) an alkaline reacting core comprising an acid-labile pharmaceutically active substance and an alkaline reacting compound different from said active substance, an alkaline salt of an acid labile pharmaceutically active substance and an alkaline reacting compound different from said active substances; (b) an inert subcoating which rapidly dissolves or disintegrates in water disposed on said core region, said subcoating comprising one or more layers comprising materials selected from the group consisting of tablet excipients, film-forming compounds and alkaline compounds; and (c) an enteric coating layer surrounding said subcoating layer, wherein the subcoating layer isolates the alkaline reacting core from the enteric coating layer such that the stability of the preparation is enhanced.

Claim 12 specifies a process for preparing an oral pharmaceutical preparation as recited in Claim 1.

III. ANALYSIS

All of the independent claims of the '505 patent and the '230 patent require the presence of "an inert subcoating" or "one or more inert reacting subcoating layers." Although the claims use varying terminology to identify the region between the "core" or "core region" and the "enteric coating" or "enteric coating layer", any intended differences are irrelevant. The claims affirmatively require that the presence of an inert subcoating layer between the surface of the core and the enteric coating and, accordingly, the terms "an inert subcoating", "one or more inert

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reacting subcoating layers" and "a separating layer" all identify the same inert subcoating layer and are used interchangeably.

Dexcel's omeprazole tablets differ from the inventions claimed in the '505 patent and the '230 patent in several particulars. Dexcel's Tablets are manufactured using conventional processing steps. The active ingredient, omeprazole, and other excipients are mixed together, compressed into tablets and then coated with an enteric coating. There is no step involving the application or formation of a subcoating or separating layer between the core and the enteric coating. Based on the aforementioned manufacturing procedure used by Dexcel to make its own omeprazole tablets there is no infringement of any of the claims of the '505 and '230 patents.

As all independent claims of the '505 and '230 patents require the presence of a subcoating or separating layer between core and the enteric coating and no such subcoating or separating layer is present in Dexcel's omeprazole tablets, there is no literal infringement of any of the claims of those patents.

Further, there is no structure in the Dexcel omeprazole tablets that could provide the basis for arguing infringement under the doctrine of equivalents. There simply is nothing in the Dexcel omeprazole tablets that performs the same function as a subcoating or separating layer, in substantially the same way to achieve substantially the same result. Indeed, no equivalent of such a claim element is present. Accordingly, there can be no infringement under the doctrine of equivalents.

IV. JURISDICTION

Dexcel hereby consents to jurisdiction in the United States District Court for the Eastern District of Virginia, Norfolk Division, solely for purposes of any infringement action based upon its aforementioned NDA. Dexcel maintains an office located at Wainwright Building, 229 West Bute Street, Suite 407, Norfolk, Virginia 23510.

V. CONCLUSION

For the reasons set forth above, Dexcel's Tablets do not infringe any of the claims of the '505 and '230 patents.

To the extent that process claims are discussed above, any such discussion is for informational purposes only. As process claims cannot be listed in the Orange Book, no certification or detailed statement regarding them is required and such claims cannot form the basis of any 30 month statutory prohibition against approval of Dexcel's NDA.

Pursuant to 21 U.S.C. § 355(c)(3)(D)(i)(III), Dexcel hereby extends Aktiebolaget Hassle and AstraZeneca an Offer of Confidential Access to Dexcel's NDA pursuant to a mutually agreeable confidentiality agreement that contains reasonable restrictions as to persons entitled to access and on the use and disposition of any information accessed.

Please be advised that Dexcel intends to obtain final approval of its NDA and proceed to market its Tablets as soon as permitted by applicable statutes and regulations.

May 4, 2006

Page 5

Dexcel expressly reserves the right to challenge the validity and enforceability of the '505 and '230 patents and/or any assertion of infringement that AstraZeneca, Aktiebolaget Hassle and/or the current owner of the '505 and '230 patents might make on new, other, or further grounds should such grounds become apparent during any ensuing litigation between the parties.

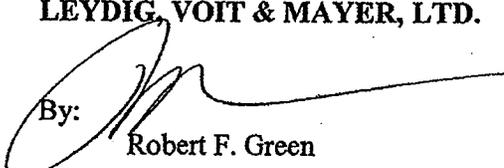
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So there is no misunderstanding, Dexcel will not only aggressively defend against any baseless lawsuit filed by Aktiebolaget Hassle or AstraZeneca, Dexcel also will seek all appropriate remedies to redress what could only be viewed as a fraudulent misuse of the '505 and '230 patents, which would harm not only Dexcel but the patients who take Prilosec® OTC tablets, resulting in antitrust liability for Aktiebolaget Hassle and AstraZeneca.

If you have any questions after reviewing this letter, please feel free to contact us to discuss this matter.

Very truly yours,

LEYDIG, VOIT & MAYER, LTD.

By: 

Robert F. Green

RFG/SSM/krs

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-032 Supplement # Efficacy Supplement Type SE-

Trade Name:
Established Name: omeprazole delayed-release tablets
Strengths: 20mg

Applicant: Dexcel Pharma Technologies Limited
Agent for Applicant: Lachman Consultants Services, Inc.

Date of Application: February 8, 2006
Date of Receipt: February 10, 2006
Date clock started after UN:
Date of Filing Meeting: March 31, 2006
Filing Date: April 11, 2006
Action Goal Date (optional): User Fee Goal Date: December 10, 2006

Indication(s) requested: Treatment of frequent heartburn (occurs 2 or more days a week)

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*
- (2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain: Prilosec OTC NDA 21229 has exclusivity until June 20, 2006

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.;
 “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge”

- Financial Disclosure forms included with authorized signature? YES NO
 (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
 NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: IND 63,799
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) October 10, 2005 NO
 If yes, distribute minutes before filing meeting.

Project Management

- Was electronic “Content of Labeling” submitted? YES NO
 If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
 YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
 N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 31, 2006

BACKGROUND: This application is for omeprazole delayed release tablet, 20mg, for the treatment of frequent heartburn (occurring 2 or more days a week). This is a 505(b)(2) application and is an omeprazole base. The Division of Nonprescription Clinical Evaluation and Division of Gastrointestinal Drug Products are the review divisions and this application will be a dual sign off by the division directors. The FDA has met with the sponsor on May 20, 2005 for a pre-NDA meeting.

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Patricia Roberts (DNCE) - safety
Secondary Medical:	Fathia Gibril (GI) - efficacy
Statistical:	Stella Grosser
Pharmacology:	N/A
Statistical Pharmacology:	
Chemistry:	Shulin Ding
Environmental Assessment (if needed):	
Biopharmaceutical:	Abimbola Adebawale
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Keith Olin
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site inspection needed? YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. inspection needed? YES NO
- PHARMACOLOGY N/A FILE REFUSE TO FILE
- GLP inspection needed? YES NO
- CHEMISTRY FILE REFUSE TO FILE
- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Keith Olin
Regulatory Project Manager, HFD-

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): 21229 – Prilosec OTC
19810 - Prilsoec

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). N/A

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Keith Olin
4/28/2006 11:52:29 AM
CSO

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA Number	22-032	Brand Name	Omeprazole Delayed-Release (Not yet determined)
OCPB Division (I, II, III)	DCP3	Generic Name	Omeprazole
Medical Division	ONP-DNCE	Drug Class	Proton Pump Inhibitor
OCPB Reviewer	Abi Adebowale	Indication(s)	Treatment of frequent heartburn (occurs 2 or more days a week)
OCPB Team Leader	Dennis Bashaw	Dosage Form	Delayed-release 20 mg tablets
Letter Date	February 8 th , 2006	Dosing Regimen	One tablet per day for a 14-day course of treatment
Stamp Date	February 10 th , 2006	Route of Administration	Oral (OTC)
Estimated Due Date of OCPB Review	September 10 th , 2006	Sponsor	Dexcel Pharma Technologies Ltd.
PDUFA Due Date	December 10th, 2006	Priority Classification	5S
Division Due Date	October 10 th , 2006	IND Number	63,799

Clin. Pharm. and Biopharm. Information

Background and Introduction: The applicant has submitted an 505(b)(2) NDA for a new formulation of omeprazole delayed release tablets which utilizes omeprazole base rather than omeprazole magnesium, which is the active ingredient of their proposed RLD, Prilosec OTC (NDA 21-229), approved for OTC marketing on June 20, 2003, for the treatment of frequent heartburn. Protocols for relative BA and food effect studies included in this NDA were found acceptable by OCPB during meetings with the sponsor on May 20th, 2005 and October 10th, 2005.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:			
gender:			
pediatrics:			
geriatrics:			
renal impairment:			
hepatic impairment:			
PD:			
Phase 2:			
Phase 3:			
PK/PD:			
Phase 1 and/or 2, proof of concept:			
Phase 3 clinical trial:			
Population Analyses -			
Data rich:			
Data sparse:			
II. Biopharmaceutics			
Absolute bioavailability:			
Relative bioavailability -			
solution as reference:			
alternate formulation as reference (IR):	X		Study # AA24171
Bioequivalence studies -			
traditional design; single / multi dose:			
replicate design; single / multi dose:			
Food-drug interaction studies:	X		Study # AA28531 (used FDA high fat diet) <i>Proposed labeling (same as Prilosec OTC) "swallow 1 tablet with a glass of water before eating in the morning"</i>
Dissolution:	X		
(IVIVC):			
Bio-wavier request based on BCS			
BCS class			
III. Other CPB Studies			
Genotype/phenotype studies:			
Other (in vitro percutaneous absorption study)			
Chronopharmacokinetics			
Pediatric development plan			
Literature References			
Total Number of Studies		2	
Filability and QBR comments			
Types and #'s of studies and supplementary information (literature review) are adequate to conduct a review	"X" if yes X	Comments Since this NDA is relying totally on the data obtained from the PK studies we will request a DSI site inspection (for both). In addition, an information request for the dissolution method development, dissolution data generated with their proposed dissolution method and their proposed acceptance criteria will be sent to the applicant.	
Application filable?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?	
Comments sent to firm?	No	Comments have been sent to firm (or attachment included). FDA letter date if applicable.	
QBR questions (key issues to be considered)	Is the new formulation of Omeprazole DR 20 mg bioequivalent to the RLD (Prilosec 20 mg OTC) under fasted conditions? Is there a food effect on the new formulation of Omeprazole DR 20 mg tablets? Is the dissolution profile of the new formulation of Omeprazole DR 20 mg tablets comparable to that of Prilosec 20 mg OTC?		

b(4)

Other comments or information not included above	None
Primary reviewer Signature and Date	Abi Adebawale 03/27/06
Secondary reviewer Signature and Date	Dennis Bashaw 03/27/06

CC: NDA 22-032, HFD-850 (P.Lee), ONP –DNCE (K. Olin), DCP 3 (D. Bashaw, J.Hunt)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Abi Adebawale
3/31/2006 10:49:31 AM
BIOPHARMACEUTICS

Dennis Bashaw
3/31/2006 05:59:15 PM
BIOPHARMACEUTICS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 5, 2006

FROM: Jacqueline A. O'Shaughnessy, Ph.D.
Sriram Subramaniam, Ph.D.
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIR covering NDA 22-032
Omeprazole 20 mg Delayed-Release Tablets, sponsored by
Dexcel Pharma

TO: Andrea Leonard Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
(DNCE)

At the request of DNCE, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence studies:

Study AA24171: Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Dexcel Ltd. 20 mg Omeprazole Delayed-Release Tablets and Procter & Gamble Co./AstraZeneca LP (Prilosec OTC™) 20.6 mg Omeprazole Magnesium Delayed-Release Tablets (equivalent to 20 mg omeprazole) in Healthy Adult Volunteers under Fasting Conditions

Study AA28531: Comparative, Randomized, Single-Dose, 2-Way Crossover Food Effect Bioavailability Study of Dexcel Ltd. 20 mg Omeprazole Delayed-Release Tablets in Healthy Adult Male Volunteers

The clinical and analytical portions of these studies were conducted at _____

_____ Please note that these pivotal studies were not subject to _____ five year

b(4)

retrospective review as they were conducted

b(4)

The current inspection (11/28-12/1/06) found that the omeprazole assay showed a non linear calibration response at the beginning of sample analysis for Study AA24171, instead of the linear response exhibited during validation. To account for the non linear response, — used a quadratic regression model. The inspection confirmed that — consistently applied a quadratic fit in all analytical runs. Following the inspection, Form FDA-483 was issued. Our evaluation of the objectionable items is as follows:

b(4)

1. The results from the original run (batch 12DAU) for subjects 30-32 in Study AA24171 were not reported although the run met the acceptance criteria. The firm's investigation fails to justify the exclusion of the entire results from the original run. There was no SOP in place to address this issue.

The results of batch 12DAU found that the omeprazole concentration at 1.25 hour for subject 32 in period 2 was BLQ (below the limit of quantitation, <2 ng/ml). This result was unexpected because the time points immediately before (hour 1) and after (hour 1.5) this sample had measurable concentrations of omeprazole (see table below).

Time (hours)	Concentration (ng/ml)
0.5	BLQ
0.75	BLQ
1	35.6
1.25	BLQ ←
1.5	116
1.75	112

— suspected that the 1 and 1.25 hour samples were switched and they conducted an investigation to confirm their suspicion. Although their investigation did not confirm that the samples were switched, — rejected the original results

b(4)

b(4)

for subjects 30-32 from batch 12DAU, reassayed the samples, and reported the repeat results. Because their investigation failed to provide justification for rejecting a passing run (batch 12DAU met the acceptance criteria), — should have reported the data from batch 12DAU and used the original concentration results for subjects 30-32 in the bioequivalence determination (see Attachment 1). **b(4)**

2. Failure to record time of placement of samples in the freezer for the 1.25 hour blood samples for subjects 1-38 (period 2) in Study AA24171. The failure was not reported in the clinical report as a discrepancy.

Although the firm needs to improve their record keeping procedures, the finding is not likely to affect the study for the following reason. The 1.25 hour plasma subject samples were reconciled and stored in the freezer 48 hours after processing. The bench-top (i.e. short-term) stability period for omeprazole in plasma (99.5 hours) covers the time elapsed between the end of sample processing and the inventory check.

Conclusions:

Following the above inspection, DSI recommends that:

- o — failed to justify the exclusion of omeprazole concentration results from analytical batch 12DAU (Item 1 above). Thus, the original results for subjects 30-32 from batch 12DAU in Study AA24171 (fasting) should have been used for the bioequivalence determination. We recommend that the biopharmaceutics reviewer evaluate the impact of using the original concentration results for these subjects on the study outcome. **b(4)**
- o The clinical portions of Studies AA24171 (fasting) and AA28531 (fed) can be considered for review.
- o The analytical portion of Study AA28531 (fed) can be considered for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Jacqueline A. O'Shaughnessy, Ph.D.

Sriram Subramaniam, Ph.D.

Final Classification:

b(4)

CC:

HFD-45/RF

HFD-48/Viswanathan/Himaya/O' Shaughnessy/Subramaniam/CF

DNCE/Olin

HFD-880 (DCP3)/Adebowale

Draft: JAO 12/4/06

Edit: SS 12/5/06

DSI: O:\BE\eircover\22032dex.omp.doc

Attachment 1 (page 1 of 3)

Original concentration results for subjects 30-32 (batch 12DAU)

Subject	Period	Sampling time	Seq. Number	Conc.	Run 12		Instrument Response
					Area	IS Area	
30	1	0	131	BLQ	0.0	187955.8	0.000000
30	1	0.25	95	BLQ	0.0	184175.1	0.000000
30	1	0.5	58	BLQ	0.0	224733.1	0.000000
30	1	0.75	24	BLQ	193.6	208578.3	0.000928
30	1	1	108	BLQ	154.7	196327.9	0.000788
30	1	1.25	138	BLQ	227.6	208784.4	0.001091
30	1	1.5	33	6.87	7373.0	216840.8	0.034002
30	1	1.75	20	19.0	19850.1	208811.5	0.093062
30	1	2	74	23.6	25351.1	214623.7	0.118119
30	1	2.333	144	74.9	70326.2	186158	0.377777
30	1	2.667	110	86.0	78514.4	181197.2	0.433561
30	1	3	135	82.0	93258.8	225645.8	0.413297
30	1	3.5	105	53.1	51741.6	193491	0.267411
30	1	4	51	32.1	33783.6	209947	0.160915
30	1	4.5	25	14.6	15928.4	210156.6	0.072938
30	1	5	15	6.20	7160.0	233673.6	0.030641
30	1	6	114	BLQ	1831.3	226095.9	0.008101
30	1	8	27	BLQ	230.9	219843.1	0.001058
30	1	10	113	BLQ	78.8	257638.8	0.008306
30	1	12	17	BLQ	0.0	230983.6	0.000000
30	2	0	48	BLQ	0.0	227443.5	0.000000
30	2	0.25	134	BLQ	0.0	230090.2	0.000000
30	2	0.5	53	BLQ	0.0	243160.6	0.000000
30	2	0.75	102	BLQ	0.0	181725	0.000000
30	2	1	130	BLQ	75.5	206240.7	0.000366
30	2	1.25	46	BLQ	296.1	219427.7	0.001349
30	2	1.5	37	25.0	25427.2	202716.9	0.125432
30	2	1.75	85	157	184087.7	231360.3	0.795675
30	2	2	7	147	163347.1	219886.3	0.744457
30	2	2.333	139	84.6	96790.8	226923.7	0.426535
30	2	2.667	147	43.6	52634.9	229751	0.229182
30	2	3	97	27.6	30808.7	222165	0.138612
30	2	3.5	97	15.3	17134.0	223684.3	0.076599
30	2	4	81	8.63	8426.1	190053.4	0.042078
30	2	4.5	70	3.23	3705.2	236051.7	0.015698
30	2	5	115	BLQ	2000.8	228872.4	0.008742
30	2	6	143	BLQ	680.4	194155.5	0.003505
30	2	8	89	BLQ	135.3	231963.2	0.000583
30	2	10	45	BLQ	0.0	229800.4	0.000000
30	2	12	30	BLQ	0.0	240482	0.000000
31	1	0	77	BLQ	0.0	218953.9	0.000000
31	1	0.25	26	BLQ	0.0	318351.1	0.000000
31	1	0.5	121	BLQ	0.0	227844.1	0.000000
31	1	0.75	36	BLQ	0.0	219718.1	0.000000
31	1	1	73	BLQ	0.0	319716.8	0.000000
31	1	1.25	69	BLQ	0.0	187807.1	0.000000
31	1	1.5	67	BLQ	0.0	208140.1	0.000000
31	1	1.75	44	BLQ	0.0	217602.1	0.000000

Attachment 1 (page 2 of 3)

Original concentration results for subjects 30-32 (batch 12DAU)

Subject	Period	Sampling time	Seq. Number	Conc.	Run 12		
					Area	IS Area	Instrument Response
31	1	2	16	BLQ	0.0	215751.7	0.000000
31	1	2.333	65	BLQ	0.0	224619.2	0.000000
31	1	2.667	42	BLQ	0.0	214682.2	0.000000
31	1	3	103	BLQ	0.0	232135	0.000000
31	1	3.5	55	BLQ	0.0	211597.1	0.000000
31	1	4	64	BLQ	192.6	221980.2	0.000868
31	1	4.5	73	BLQ	1982.2	224933.7	0.008812
31	1	5	117	352	483840.2	224046.1	1.802487
31	1	6	116	93.9	104068.2	219583.2	0.473935
31	1	8	126	9.10	9422.0	208188.1	0.045257
31	1	10	88	BLQ	1938.8	228903.9	0.008470
31	1	12	14	BLQ	1068.4	194888	0.005483
31	2	0	93	BLQ	0.0	187060.7	0.000000
31	2	0.25	118	BLQ	213.4	200628.6	0.001064
31	2	0.5	120	64.1	63788.9	203683.9	0.322992
31	2	0.75	63	486	412140.6	197852.1	2.003074
31	2	1	98	478	334404.3	217081.8	2.461785
31	2	1.25	128	321	338202.5	206382.9	1.638714
31	2	1.5	99	203	203467.5	196678.4	1.029434
31	2	1.75	91	144	164384.0	225984	0.728299
31	2	2	145	93.8	98074.3	207181.9	0.473373
31	2	2.333	32	71.2	72787.8	202812.1	0.358893
31	2	2.667	86	47.9	48254.2	200461.6	0.240715
31	2	3	38	34.5	38431.2	222033.3	0.173088
31	2	3.5	94	22.2	22900.3	205559.6	0.111405
31	2	4	23	15.2	14951.0	196761.5	0.075985
31	2	4.5	96	8.32	8611.9	208404.7	0.041323
31	2	5	82	5.16	5430.0	214613.3	0.025395
31	2	6	36	2.38	2264.9	198125.6	0.011432
31	2	8	84	BLQ	564.6	199313.7	0.003149
31	2	10	6	BLQ	289.4	226272	0.001279
31	2	12	101	BLQ	85.2	228056.1	0.000374
32	1	0	146	BLQ	0.0	164390.1	0.000000
32	1	0.25	21	BLQ	0.0	200194.1	0.000000
32	1	0.5	111	BLQ	185.6	186609.7	0.001000
32	1	0.75	76	BLQ	755.0	211081	0.003577
32	1	1	10	4.49	3523.0	199959.8	0.022037
32	1	1.25	140	32.4	30489.2	187645.5	0.162483
32	1	1.5	65	97.1	96661.3	197133.3	0.490335
32	1	1.75	124	158	160907.7	209110.3	0.798180
32	1	2	8	136	113529.0	163479.6	0.680060
32	1	2.333	106	66.9	54470.2	161733.8	0.336789
32	1	2.667	80	35.9	38149.3	211790.2	0.180128
32	1	3	28	19.8	20166.8	203484.7	0.099107
32	1	3.5	109	12.6	12023.5	194973.2	0.061663
32	1	4	43	5.95	5932.8	201778.6	0.028405
32	1	4.5	13	3.48	3610.2	213353.2	0.016063
32	1	5	19	BLQ	1279.9	213883.9	0.003984

Attachment 1 (page 3 of 3)

Original concentration results for subjects 30-32 (batch 12DAU)

Subject	Period	Sampling time	Seq Number	Conc.	Run 12		
					Area	IS Area	Instrument Response
32	1	6	49	BLQ	541.5	217136.8	0.002494
32	1	8	87	BLQ	83.7	227109.5	0.000369
32	1	10	62	BLQ	51.2	213338	0.000240
32	1	12	92	BLQ	0.0	211984	0.000000
32	2	0	100	BLQ	0.0	215291.2	0.000000
32	2	0.25	18	BLQ	0.0	208141.3	0.000000
32	2	0.5	31	BLQ	0.0	200467.3	0.000000
32	2	0.75	59	BLQ	392.0	201239.4	0.000954
32	2	1	52	116	112119.1	191777.7	0.584631
32	2	1.25	107	BLQ	0.0	219937.2	0.000000
32	2	1.5	123	116	112119.1	191777.7	0.584631
32	2	1.75	129	112	124144.2	218768.3	0.587625
32	2	2	11	70.0	74080.6	209920	0.352899
32	2	2.333	125	70.0	74080.6	209920	0.352899
32	2	2.667	30	46.1	45392.1	195911.7	0.231697
32	2	3	122	31.5	35855.3	226898.9	0.156023
32	2	3.5	136	16.5	18503.6	224881.4	0.082282
32	2	4	137	12.5	11795.8	188614.8	0.062539
32	2	4.5	133	6.02	6654.3	223851.1	0.029727
32	2	5	79	4.39	4848.1	225282.2	0.021520
32	2	6	61	BLQ	1940.1	248815.1	0.007797
32	2	8	9	BLQ	473.5	235831.5	0.002008
32	2	10	40	BLQ	230.3	204473.7	0.001127
32	2	12	71	BLQ	90.2	184992.4	0.000488

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this page is the manifestation of the electronic signature.**

/s/

Jacqueline OShaughnessy

12/5/2006 03:13:00 PM

PHARMACOLOGIST

The paper copy was signed by Drs. Viswanathan, Subramaniam,
and O'Shaughnessy on Dec 5, 2006.

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N22032

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ACTION PACKAGE CHECKLIST

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Application Information		
BLA # NDA # 22-032	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: omeprazole 20mg Delayed-Release Established Name: none Dosage Form: tablet		Applicant: Dexcel Pharma LTD
RPM: Keith Olin	Division: 560	Phone # 301-796-0962
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 21-229 Prilosec OTC NDA 19-810 Prilosec (RX) Provide a brief explanation of how this product is different from the listed drug. This product is a different salt base. <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date		December 4, 2007
❖ Action Goal Date (if different)		
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA X AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input type="checkbox"/> None 12/8/06, 06/14/07
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input checked="" type="checkbox"/> OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p>	<p>12/6/06 - J. Korvick 12/7/06, 06/12/07; 12/04/07 - A. Leonard-Segal</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p>	<p>N/A</p>
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>11/28/07</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	<p>12/7/06, 06/04/07, 11/28/07</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	<p>12/7/06, 06/04/07, 11/28/07</p>

❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input checked="" type="checkbox"/> Other reviews 11/17/06; 12/8/06,05/29/07, 06/11/07, 12/3/07 <input type="checkbox"/> Memos of Mtgs
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Administrative Documents

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	4/28/06 RPM; 03/29/06 CMC; 3/31/06 Biopharm
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> • Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) • Incoming submission documenting commitment 	<input checked="" type="checkbox"/> None
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	12/6/06; 06/9/06; 04/11/06; 08/28/06; 09/22/06; 11/21/06; 12/6/06; 12/8/06; 12/07/07;05/1/07; 11/20/07
❖ Internal memoranda, telecons, email, etc.	12/7/06 -CMC
❖ Minutes of Meetings <ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) • Pre-NDA/BLA meeting (<i>indicate date</i>) • EOP2 meeting (<i>indicate date</i>) • Other (e.g., EOP2a, CMC pilot programs) 	<input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> No mtg
❖ Advisory Committee Meeting <ul style="list-style-type: none"> • Date of Meeting • 48-hour alert or minutes, if available 	<input checked="" type="checkbox"/> No AC meeting
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information

❖ CMC/Product review(s) (<i>indicate date for each review</i>)	12/7/06; 12/05/06, 02/22/07, 10/30/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> • <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) 	

• <input type="checkbox"/> Review & FONSI (indicate date of review)	
• <input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (indicate date(s)) • Compliance Status Check (approvals only, both original and supplemental applications) (indicate date completed, must be within 60 days prior to AP) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	10/03/06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	11/20/06 (GI); 11/9/06 (OTC); 12/4/06 (OTC), 06/04/07 (OTC), 11/21/07 (OTC)
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	N/A
❖ Clinical consult reviews from other review disciplines/divisions/Centers (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (indicate location/date if incorporated into another review)	
❖ Risk Management Plan review(s) (including those by OSE) (indicate location/date if incorporated into another review)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested
• Clinical Studies	
• Bioequivalence Studies	12/5/06
• Clin Pharm Studies	
❖ Statistical Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 12/7/06,06/1/07

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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this page is the manifestation of the electronic signature.**

/s/

Keith Olin
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