Endo
100 Endo Boulevard
Chadds Ford, PA 19317
610.558.9800
484 840.4290 fax

endo.com

endo

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August 10, 2012

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

CITIZEN PETITION

Endo Pharmaceuticals Inc. ("Endo") submits this Citizen Petition under Sections 505(j) and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and in accordance with the Food and Drug Administration's ("FDA's" or the "Agency's") implementing regulations set forth at 21 C.F.R. § 10.30 and 21 C.F.R. § 314.161 to request that the Commissioner of Food and Drugs take the actions described below with respect to Endo's discontinued Opana® ER (oxymorphone HCl) Extended-release Tablets approved under New Drug Application ("NDA") No. 021610 and any pending or approved Abbreviated New Drug Applications ("ANDAs") for which Opana® ER approved under NDA No. 021610 serves as the Reference Listed Drug ("RLD").

I. ACTION REQUESTED

Endo requests that FDA:

(1) Determine that the discontinued, non-crush-resistant version of Opana® ER approved under NDA No. 021610 was discontinued for reasons of safety and can no longer serve as an RLD for an ANDA applicant;

(2) Refuse to approve any pending ANDA for a generic version of the non-crush-resistant version of Opana® ER approved under NDA No. 021610; and

(3) Suspend and withdraw the approval of any ANDA referencing Opana® ER approved under NDA No. 021610 as the RLD.

FDA-2012-P-0895

2012-6165 CP

II. STATEMENT OF GROUNDS

A. Factual Background

1. Opioid analgesics

Opioid analgesics, such as oxycodone, oxymorphone, morphine, hydromorphone and methadone, are effective in the treatment of chronic and moderate to severe pain, but abuse of prescription opioid analgesics is "at the center of a major public health crisis of addiction, misuse, abuse, overdose and death."[1] The number of first-time abusers of prescription opioids rose from 628,000 in 1990 to 2.4 million in 2004.[2] Prescription opioid-related deaths in 2008 have nearly quadrupled from 1999 figures, according to the Center for Disease Control and Prevention.[3] Over a five-year period, the number of estimated emergency department visits related to opioid analgesic abuse more than doubled from 144,644 in 2004 to 305,885 in 2008, an increase of 111 percent.[4] Data from the Researched Abuse, Diversion and Addiction-Related Surveillance system

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1 FDA, Opioid Drugs and Risk Evaluation and Mitigation Strategies (REMS), available at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

2 See Jane C. Ballantyne, U.S. Opioid Risk Management Initiatives, Int'l Assoc. for the Study of Pain, Clinical Updates, Vol. 17, Issue 6, at 1 (2009), available at http://www.iasp-pain.org/AM/AMTemplate.cfm?Section=Home&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=15080&SECTION=Home; Andrew Rosenblum et al., Opioids and the Treatment of Chronic Pain: Controversies, Current Status, and Future Directions, 16(5) Exp. Clin. Psychopharmacol. 405, 406 (2009), available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2711509/pdf/nihms97365.pdf; Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA), Patterns and Trends in Nonmedical Prescription Pain Reliever Use: 2002 to 2005, The National Survey on Drug Use and Health Report (April 6, 2007), available at http://www.samhsa.gov/data/2k7/Pain/Pain.pdf.

3 See Centers for Disease Control and Prevention, Vital Signs: Overdoses of Prescription Opioid Pain Relievers – United States, 1999-2008, 60 Morbidity and Mortality Weekly Report, at 3 (Nov. 1, 2011), available at http://www.cdc.gov/mmwr/PDF/wk/mm60e1101.pdf.

4 See SAMHSA, Trends in Emergency Department Visits Involving Nonmedical Use of Narcotic Pain Relievers, The Drug Abuse Warning Network Report, at 2 (June 18, 2010), available at http://oas.samhsa.gov/2k10/DAWN016/OpioidEdHTML.pdf.

("RADARS") in 2010 indicate that prescription opioid abuse, misuse and diversion rates continue to increase.[5]

In response to these public health concerns, FDA has undertaken numerous initiatives to prevent opioid misuse and abuse, including the release of a class-wide Risk Evaluation and Mitigation Strategy ("REMS") for all extended-release opioid medications, which was in development between the Agency and stakeholders since at least November 2009 and recently finalized.[6] Implementation of the REMS should mitigate abuse and misuse of prescription opioid analgesics. As FDA recognizes, however, more action is needed to reduce abuse and misuse. The Agency "has been looking for novel interventions to prevent [opioid] abuse" and supports the development of drug products with abuse deterrent properties.[7]

In addition to FDA, Congress has also recognized the need to address the public health concern involving opioid analgesics. Specifically, Congress has encouraged the development of drugs with abuse-resistant characteristics and directed FDA to expedite the filing and review of such drugs.[8] Congress has also encouraged dissemination of information that differentiates these drugs.[9]

2. Opana® ER Regulatory History and Background

FDA approved NDA No. 021610 for Opana® ER (oxymorphone HCl) Extended-release Tablets on June 22, 2006 for the management of moderate to severe pain in patients requiring an around-the-clock opioid analgesic. Opana® ER under NDA No. 021610 was marketed in 5 mg, 7.5 mg, 10, mg, 15 mg, 20 mg, 30 mg, and 40 mg

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5 See RADARS® System 5th Annual Meeting Slides (Apr. 28, 2011), available at http://www.radars.org/Portals/1/Dart-1.pdf.

6 See FDA, Opioid Drugs and REMS, supra note 1; FDA, Blueprint for Prescriber Continuing Education Program (Oct. 25, 2011); FDA, Opioid and REMS: November 2009 Update.

7 Memorandum from Bob A. Rappaport, M.D., Director, Division of Anesthesia and Analgesia Products, Office of Drug Evaluation II, CDER, FDA, to the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, as part of the April 22, 2010 Advisory Committee Meeting Background Materials, at 1 (Mar. 26, 2010).

8 See S. Rep. No. 109-266, at 142 (2006).

9 See H. Rep. No. 109-102, at 81 (2005).

strengths. Oxymorphone (14-hydroxydihydro-morphinone) is a semi-synthetic opioid analgesic that is structurally related to morphine and is a metabolite of oxycodone. It is controlled under Schedule II of the Controlled Substances Act.[10]

Endo subsequently developed a crush-resistant version of Opana® ER in order to offer a meaningful benefit in reducing the potential for abuse, misuse and diversion as compared to non-crush-resistant products. Endo submitted NDA No. 201655 to FDA on July 7, 2010 for the company's new design of Opana® ER incorporating physical and physiochemical barriers to tampering (referred to as "Opana® ER Crush-Resistant Formulation" or "Opana® ER CRF").[11] Opana® ER CRF contains oxymorphone embedded in a hard polyethylene oxide matrix that is resistant to crushing. The manufacturing process for Opana® ER CRF imparts mechanical strength to the tablets through a heat extrusion process. Characteristics of the tablets include high breaking force that resists crushing and pulverizing, and resistance to aqueous extraction (i.e., poor syringeability). FDA approved NDA No. 201655 for Opana® ER CRF on December 9, 2011. Opana® ER CRF is approved in 5 mg, 7.5 mg, 10, mg, 15 mg, 20 mg, 30 mg, and 40 mg strengths. The 7.5 mg and 15 mg strengths are not currently marketed.

Opana® ER CRF offers resistance to crushing, which can deter abuse where recreational and experienced abusers attempt to crush the tablets for ingestion or further manipulation. The tablets also offer resistance in situations of misuse – for example, where patients or healthcare providers attempt to crush tablets to facilitate swallowing or gastric tube administration, where patients intentionally or unintentionally attempt to

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[10] FDA also approved an immediate-release formulation of Opana® Tablets (NDA No. 021611) on June 22, 2006. Oxymorphone immediate-release tablets were previously approved and marketed in the early 1960s but were removed from the market for commercial reasons. Opana® is also available in an injectable dosage form (NDA No. 011707).

[11] FDA's draft guidance on abuse potential of new drugs refers to "[f]ormulations that deter abuse," including those that have "physical barriers to tampering," as "abuse deterrent formulations." FDA Draft Guidance for Industry, Assessment of Abuse Potential of Drugs, at 8 (Jan. 2010). Endo uses the term "crush-resistant" rather than "abuse deterrent" to reflect that the new design of Opana® ER is more resistant to crushing, which serves as an impediment to both intranasal and intravenous abuse. Crushing tablets is the preferred method by which abusers prepare oxymorphone tablets for administration. See Stephen F. Butler et al., Abuse Risks and Routes of Administration of Different Prescription Opioid Compounds and Formulations, 8 Harm Reduction J. 1, 14 (2011) (Attachment 1).

chew the tablets to facilitate swallowing or where children unintentionally chew the tablets prior to an accidental ingestion.

Endo recently discontinued from sale for safety reasons all strengths of Opana® ER approved under NDA No. 021610 and notified FDA of the discontinuation. As a result, FDA moved Opana® ER to the Discontinued List section of the Agency's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"). Opana® ER CRF (NDA No. 201655) remains in the Prescription Drug Product List section of the Orange Book and is the only currently marketed Opana® ER drug product.

Prior to FDA's approval of NDA No. 201655 for Opana® ER CRF, and prior to the discontinuation of Opana® ER approved under NDA No. 021610, FDA approved two ANDAs for generic versions of Opana® ER that cite NDA No. 021610 as their respective RLD. Specifically, FDA approved Impax Laboratories' ("Impax's") ANDA No. 079087 on December 21, 2010 for all Opana® ER strengths, and Actavis South Atlantic LLC's ("Actavis'") ANDA No. 079046 on December 13, 2010 for the 7.5 mg and 15 mg strengths of Opana® ER. Because both ANDAs are directed to the original Opana® ER NDA, none of the drug products approved under either application likely have a crush-resistant design.

Under a patent license agreement with Endo, the earliest time by which Impax could come to market with its non-crush-resistant formulation is January 1, 2013. Thus, the issues raised in this petition are of immediate importance.

3. Applicable Law

FDA's regulations implementing the FDC Act require the Agency to determine – either on FDA's own initiative or in response to citizen petition – "whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons. . . ."[12] FDA must make such a determination prior to approving a pending ANDA that refers to the discontinued drug, and "[w]henever a listed drug is voluntarily withdrawn from sale and [ANDAs] that referred to the listed drug have been approved." See id. Pursuant to recent amendments made to the FDC Act by the FDA Safety and Innovation Act ("FDASIA"),[13] FDA must issue a final, substantive determination on a petition submitted pursuant to 21 C.F.R. § 314.161(b) "no later than 270 days after the

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[12] 21 C.F.R. §§ 314.161(a), (b).

[13] Pub. L. No. 112-144, 126 Stat. 993 (2012).

date the petition is submitted." FDC Act § 505(w), as amended by FDASIA § 1134(a). The new requirement applies to any petition that is submitted pursuant to 21 C.F.R. § 314.161(b) on or after July 9, 2012.[14]

Under FDC Act § 505(j)(4)(I) and FDA's implementing regulations at 21 C.F.R. § 314.127, FDA may refuse to approve an ANDA if the Agency determines that the RLD was withdrawn from sale for reasons of safety or effectiveness. If FDA makes such a determination, then the RLD is removed from the Orange Book.[15] In addition, FDA can suspend and withdraw approval of an ANDA if the Agency determines that the RLD was withdrawn from sale for reasons of safety or effectiveness.[16]

B. Opana® ER (NDA No. 21610) Was Discontinued from Sale for Reasons of Safety

Endo requests that FDA determine that Opana® ER approved under NDA No. 021610 was discontinued from sale for safety reasons. Upon making such a determination, FDA must remove the product from the Orange Book and should take appropriate action with respect to pending and approved ANDAs that cite Opana® ER as the RLD. Endo also requests that FDA promptly make such decisions. The potential widespread availability of non-tamper-resistant generics of all strengths of Opana® ER in early 2013 calls into question whether these generics can be properly marketed in view of the discontinuation of Opana® ER for safety reasons.

The intent of the manufacturer is a "focus" of FDA's decision on whether a drug was discontinued from sale for reasons of safety or effectiveness.[17] FDA discerns the actual intent of the manufacturer based on the reasons given by the manufacturer,

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[14] See FDASIA § 1134(b). FDASIA also amended FDC Act § 505(q) to require FDA to respond to certain petitions, including petitions affecting pending ANDAs, within 150 days after receiving such a petition. See FDASIA § 1135. Insofar as FDA considers this petition to be a petition covered by FDC Act § 505(q), then Endo expects FDA to take final agency action prior to the 270-day timeframe required by FDC Act § 505(w). In either case, Endo requests that FDA make a final determination with respect to the issues raised in this petition prior to the January 1, 2013 date on which an ANDA sponsor could begin marketing its generic version of Opana® ER approved under NDA No. 021610.

[15] FDC Act § 505(j)(7)(C); see also 21 C.F.R. § 314.162.

[16] FDC Act § 505(j)(6); see also 21 C.F.R. §§ 314.150, 314.151, 314.153.

[17] FDA, Proposed Rule, ANDA Regulations, 54 Fed. Reg. 28,872, 28,907 (July 10, 1989).

whether the manufacturer had concerns with safety or effectiveness of the product, and "circumstantial evidence and logical inference."[18] For example, in 1986, Hoechst-Roussel discontinued the antidepressant Merital (nomifensine maleate) from sale "as a precautionary measure" due to increased reports of serious hypersensitivity reactions occurring in patients in the United Kingdom.[19] FDA "confirmed that the manufacturer's decision to withdraw the product from sale was base[d] on safety concerns," and, "[a]s a consequence," FDA removed nomifensine maleate from the list of approved drugs.[20] Similarly, in deciding that Janssen Pharmaceutical discontinued Hismanal (astemizole) 10 mg tablets for reasons of safety, FDA "considered the sponsor's explanation of the basis for the withdrawal of the product and information available to the agency regarding Hismanal."[21]

Endo discontinued Opana® ER (NDA No. 021610) for reasons of safety. While Opana® ER is safe and effective when taken as prescribed, it was nevertheless subject to abuse, misuse and diversion. And recent data and reports suggest that rates of abuse, misuse, and diversion of opioid analgesics, such as Opana® ER, continue to rise.[22] Notably, abuse of extended-release oxymorphone has risen by approximately 139% since the introduction of abuse-deterrent OxyContin (oxycodone HCl) on the market in 2010.[23] This suggests that, among intentional abusers of opioids, the difficulty in abusing the new formulation of OxyContin has driven abusers to formulations that lack similar abuse-deterrent technologies. The increase in Opana® ER abuse rates are attributed to the ease of defeating the extended release properties of Opana® ER.[24] The recent spike in Opana®

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18 Id.

19 FDA, Removal of Nomifensine Maleate From List of Approved Drug Products, 51 Fed. Reg. 21,981, 21,982 (June 10, 1986).

20 Id.

21 FDA, Determination That Astemizole 10-Milligram Tablets Were Withdrawn From Sale for Safety Reasons, 64 Fed. Reg. 45,973 (Aug. 23, 1999).

22 See RADARS System Slides, supra note 5.

23 R. Black et al., Effects of Reformulated OxyContin® Among Patients Assessed for Substance Abuse Treatment in the NAVIPPRO Sentinel Surveillance Network, American Pain Society 31st Annual Scientific Meeting Abstract (Apr. 2012), available at http://www.ampainsoc.org/abstract/view/5104/.

24 See, e.g., Drug Enforcement Agency, Philadelphia Division Intelligence Program, Drug Intelligence Brief: Opana (Oxymorphone) Abuse (May 2011) ("Users are reportedly switching from Oxycontin to Oxymorphone for ease of use (crushable)"), available at http://www.justice.gov/dea/pubs/states/phila_opana.pdf; New York Nassau County,

ER abuse has been accompanied by a rise in overdoses from Opana® ER.[25] Non-crush-resistant formulations are becoming increasingly attractive targets of abuse and diversion.

Endo remains committed to addressing patient safety and appropriate uses of opioids. Endo developed Opana® ER CRF to provide a crush-resistant product, equally as effective as Opana® ER, which would discourage abuse, misuse and diversion. Endo devoted extensive resources to develop Opana® ER CRF. Because Opana® ER presents a greater risk of abuse, misuse and diversion than Opana® ER CRF, Endo discontinued Opana® ER from sale for safety reasons within the meaning of FDC Act § 505(j)(7)(C) and 21 C.F.R. § 314.161.

Opana® ER CRF provides safety advantages over Opana® ER. It is resistant to crushing by common methods and tools employed by abusers of prescription opioids. The presence of both Opana® ER CRF and generic, non-crush-resistant oxymorphone formulations on the market simultaneously would allow abuse or diversion to continue, limiting the potential benefits that can be provided by Opana® ER CRF. Furthermore, Opana® ER CRF is less likely to be chewed or crushed even in situations where there is no intent for abuse, such as where patients inadvertently chew the tablets, or where caregivers attempt to crush the tablets for easier administration with food or by gastric tubes, or where children accidentally gain access to the tablets. The new formulation reduces the risk of an immediate release of a potentially lethal dose of oxymorphone in these situations.

FDA has previously compared the safety risks of a discontinued product with its closest substitute to determine whether the withdrawn product was discontinued for reasons of safety. For example, when FDA determined that HalfLytely Bisacodyl Tablet Bowel Prep Kit, 10 mg, was discontinued for safety or effectiveness reasons after the NDA-holder, Braintree Laboratories, received approval for a 5 mg version of the product, the Agency took into consideration the safety advantages of the newer 5 mg version. Data comparing the 5 mg and 10 mg versions of the product showed comparable

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Mangano Issues Dependency Public Health Alert On Increasing Usage Of The Narcotic Drug Opana (May 2011), available at http://www.nassaucountyny.gov/agencies/CountyExecutive/NewsRelease/2010/5-9-2011.htm; Donna Leinwand Leger, Opana Abuse in USA Overtakes OxyContin, USA Today (July 10, 2012), available at http://www.usatoday.com/news/nation/story/2012-07-10/opana-painkiller-addiction/56137086/1.

[25] See Leinwand, supra note 24.

effectiveness, however, the 5 mg product had "a safety advantage over the 10-mg product because there is less abdominal fullness and cramping . . . ."[26] When FDA concluded that Brevibloc (esmolol HCl), 10 mL ampule concentrate, was discontinued for reasons of safety because the product posed a higher risk of medication errors that could lead to serious outcomes, the Agency took into account that "alternative presentations of the product," like a ready-to-use vial, were available that did not have the same potential for medication errors.[27]

From a risk management perspective, when a product is introduced by a sponsor that is ***more safe*** than its discontinued predecessor product, that safety advantage should be considered by FDA in determining why the product was discontinued. FDA's practice reflects that it will consider comparative safety advantages offered by an alternative product. Furthermore, FDA considers risks from products used in contravention to their labels when deciding whether a product was discontinued for safety reasons.[28] For example, in July 2005, FDA suspended marketing of Palladone (hydromorphone HCl) Extended-release Capsules due to the "potential for severe side effects" when Palladone

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[26] FDA, Determination That Halflytely and Bisacodyl Tablets Bowel Prep Kit (Containing Two Bisacodyl Delayed Release Tablets, 5 Milligrams) Was Withdrawn From Sale for Reasons of Safety or Effectiveness, 76 Fed. Reg. 51,037 (Aug. 17, 2011).

[27] See FDA, Determination That BREVIBLOC (Esmolol Hydrochloride) Injection, 250 Milligrams/Milliliter, 10-Milliliter Ampule, Was Withdrawn From Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. 24,710, 24,711 (May 5, 2010); see also FDA, Determination That Halflytely and Bisacodyl Tablets Bowel Prep Kit (Containing Two Bisacodyl Delayed Release Tablets, 5 Milligrams) Was Withdrawn From Sale for Reasons of Safety or Effectiveness, 76 Fed. Reg. 51,037 (Aug. 17, 2011).

[28] The approved conditions of use do not limit FDA's safety determination. FDC Act § 505(e) describes when FDA may withdraw an application for safety reasons related to the application's "conditions of use" after notice and opportunity for a hearing. FDC Act § 505(e). The grounds described in Section 505(e) for withdrawal of a drug are distinct from a determination by FDA that a drug has been withdrawn by the manufacturer for reasons of safety or effectiveness. See FDC Act § 505(j)(6) (an ANDA cannot be approved if the listed drug was withdrawn by FDA on grounds described in Section 505(e) "***or*** was withdrawn or suspended under this paragraph *or* which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons") (emphases added); § 505(j)(7) (FDA shall remove a drug from the list of approved drugs if the drug was withdrawn by FDA on grounds described in Section 505(e) "***or*** was withdrawn or suspended under paragraph (6) *or* if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons") (emphases added).

is taken with alcohol.[29] Although the Palladone label in numerous places directed patients not to combine the drug with alcohol and warned providers of the effects of alcohol, the potential for severe side effects due to "dose dumping" led FDA to suspend marketing and sales of the drug.[30]

Opana® ER CRF provides safety advantages over Opana® ER based on the *in vitro* and bioavailability data and studies involving experienced opioid abusers provided by Endo to FDA. The sudden and dramatic increase in abuse and overdose of non-crush-resistant oxymorphone formulations following the introduction of a tamper-resistant formulation of OxyContin also demonstrate that these formulations are less safe than Opana® ER CRF.

C. Conclusion

For the reasons set forth above, FDA should determine that Opana® ER was discontinued for safety reasons in light of Endo's intent in discontinuing Opana® ER and in light of the crush-resistance and attendant safety advantages provided by Opana® ER CRF in comparison to the original formulation and remove the product from the Orange Book. Upon determining that Opana® ER was discontinued for safety reasons, FDA should refuse to approve any pending ANDA for a generic version of the drug and promptly move to suspend and withdraw the approval of any ANDA referencing Opana® ER (NDA No. 021610) as the RLD.

III. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

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[29] FDA Public Health Advisory: Suspended Marketing of Palladone (hydromorphone hydrochloride, extended-release capsules) (July 13, 2005), available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051743.htm.

[30] Palladone Prescribing Information, at 14, 15, 17, 18 (Sept. 2004), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/021044lbl.pdf.

IV. ECONOMIC IMPACT STATEMENT

Petitioner will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

V. CERTIFICATIONS

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

Endo makes the following certification pursuant to FDC Act § 505(q)(1)(H): I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: May 31, 2012. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Endo. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Robert Barto/prc

Robert Barto
Vice President, Regulatory Affairs
Endo Pharmaceuticals Inc.

Attachment