**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

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| MYLAN PHARMACEUTICALS INC.<br><br>and<br><br>MATRIX LABORATORIES LTD.<br><br>Plaintiffs,<br><br>v.<br><br>UNITED STATES FOOD AND DRUG ADMINISTRATION<br><br>Defendant. | Case No. 1:11-cv-00566-RWR<br>(REDACTIONS UNDER SEAL) |

**PLAINTIFFS' MEMORANDUM IN SUPPORT OF MOTION FOR A PRELIMINARY INJUNCTION**

March 24, 2011

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| MYLAN PHARMACEUTICALS INC., and MATRIX LABORATORIES LTD., Plaintiffs, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, Defendant. | Case No. 1:11-cv-00566-RWR |

**PLAINTIFFS' MEMORANDUM IN SUPPORT OF MOTION FOR A PRELIMINARY INJUNCTION**

## I. PRELIMINARY STATEMENT

LIPITOR® (atorvastatin calcium), a prescription drug used primarily to treat high cholesterol, is one of the most widely used and prescribed drugs in the United States, with annual sales of over $7 billion, and over two billion doses prescribed annually. LIPITOR® currently has no generic competitors, and has enjoyed a robust 15 years of sales in the United States without generic competition. The arbitrary, capricious and unlawful actions of the U.S. Food and Drug Administration ("FDA" or "the Agency") are stalling early entry of generic companies to this vitally important market, at great cost to potential generic competitors (including Plaintiffs) and the American public.

LIPITOR® is fast approaching the end of brand-name market exclusivity, and numerous generic drug manufacturers, including Plaintiffs Mylan Pharmaceuticals Inc. ("Mylan") and Matrix Laboratories Ltd. ("Matrix"), are awaiting FDA approvals for their generic versions of atorvastatin calcium. When generic LIPITOR® becomes available to the market, the drug's cost to the public will be radically reduced. Annual savings for all United States payors for the generic version of LIPITOR® are estimated to reach between $3.9 billion and $6.7 billion per year, which equals a savings of between $10.9 million and $18.3 million per day. Federal payors alone, such as Medicare, Medicaid and the Department Veterans Affairs, could save between $1.3 and $2.3 billion in the first year after the launch of this generic product.

While there are at least seven companies that have submitted generic drug applications (referred to as Abbreviated New Drug Applications, or "ANDAs") to market their versions of LIPITOR®, at present none of these products can reach the market until 180 days after commercial launch by the first generic company to have submitted an ANDA for a generic version of LIPITOR® containing a certification challenging a patent for LIPITOR® unless FDA rejects that company's ANDA. And, although FDA has all the information necessary to determine whether that ANDA should be denied or deemed withdrawn (opening up generic competition in the atorvastatin market much sooner than expected), FDA has unreasonably and unlawfully failed to issue a decision.

Ranbaxy Laboratories Limited ("Ranbaxy") was the first company to submit an ANDA for a generic version of LIPITOR® containing a certification challenging a patent.

On information and belief, Ranbaxy's atorvastatin was developed at Ranbaxy's manufacturing facility in Paonta Sahib, India (hereinafter, "Ranbaxy's ANDA"). Because its generic LIPITOR® ANDA was the first relevant filed ANDA, Ranbaxy was entitled to a 180-day period of marketing exclusivity upon FDA approval. However, in February 2009, FDA invoked its Application Integrity Policy ("AIP") with regard to certain ANDAs developed by Ranbaxy at the Paonta Sahib site and submitted for FDA approval. FDA determined that Ranbaxy "submitted untrue statements of material fact" in certain unidentified ANDAs. FDA advised Ranbaxy that the Agency was invoking the AIP. Only FDA and Ranbaxy know with certainty what applications are subject to the AIP.

According to the applicable statutory scheme, the terms of the AIP, and, indeed, FDA's communication to Ranbaxy, the AIP requires FDA to reject any pending ANDA tainted by unreliable or false data. So, if Ranbaxy's ANDA is tainted by unreliable data and subject to the AIP, FDA must reject Ranbaxy's ANDA, and determine that Ranbaxy has lost any 180-day marketing exclusivity. Upon such a determination by FDA, other generic manufacturers, including Plaintiffs, could be able to commercially launch their generic atorvastatin products as early as June 28, 2011, following the expiration of pediatric exclusivity applicable to certain patents for LIPITOR®. But until FDA acts – one way or the other – manufacturers cannot prepare for a commercial launch without risking investments worth tens of millions of dollars in generic product production and wasting countless other resources, all of which can never be recouped. FDA must make a decision soon on Ranbaxy's exclusivity period so that, if the AIP is applicable to the

Ranbaxy atorvastatin ANDA, the public can reap earlier benefits of lower-cost generic alternatives to this expensive but important brand-name drug, and the irreparable harm suffered by Plaintiffs and perhaps by other generic applicants can be terminated.

FDA's inexplicable inaction and silence – refusing even to say whether Ranbaxy's generic LIPITOR® ANDA is among the ANDAs subject to the AIP – arbitrarily denies Plaintiffs and other generic manufacturers their economic and other rights to enter a valuable market, and injures the public by denying it access to more affordable drugs that are necessary for public health. This Court should prevent that harm from being compounded by further unlawful Agency delay. Plaintiffs request that the Court order FDA to promptly issue a decision whether the AIP applies to the Ranbaxy ANDA, and, if so, whether Ranbaxy maintains entitlement to a 180-day exclusivity period that will further delay final approval of ANDAs submitted by Plaintiffs and other generic drug manufacturers.

## II. STATEMENT OF FACTS

### A. Interested Parties

Plaintiffs Mylan and Matrix manufacture and market generic drugs, and Matrix has pending at FDA an ANDA for approval of atorvastatin calcium, which is a generic form of LIPITOR®, the brand name drug marketed by Pfizer Inc. ("Pfizer"). Declaration of Dr. Hari Babu ("Babu Decl.") ¶ 4; Declaration of Anthony Mauro ("Mauro Decl.") ¶ 3.

Defendant, FDA, is charged with administering the Federal Food, Drug, and Cosmetic Act ("FDC Act" or "FDCA"), and has regulatory and statutory authority over the process of new drug approvals. FDA promulgated a policy known as the AIP in 1991, which established for the pharmaceutical industry, the market, and the public at large what sanctions can be expected from the Agency when false or unreliable data or information is detected in submissions to the Agency in connection with applications. *See* FDA Final Policy on "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities," 56 Fed. Reg. 46,191 (Sept. 10, 1991), Declaration of Karla Palmer ("Palmer Decl.") Ex. A.

Ranbaxy manufactures generic drugs, and also has a pending ANDA for a formulation of atorvastatin. Upon information and belief, Ranbaxy's ANDA is subject to FDA's AIP.[1]

**B. Regulatory Background**

The approval of generic drugs is governed by the FDC Act, as modified by the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Act" or "Hatch-Waxman Amendments") and the Medicare Modernization Act ("MMA"). *See* 21 U.S.C. § 355 *et. seq.*;[2] Mylan Pharm., Inc. v. Shalala, 81 F. Supp. 2d 30, 31

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1 The generic drug approval process largely protects generic drug applicants' information from public disclosure, so Plaintiffs are unable to access the ANDA submitted by Ranbaxy for atorvastatin. However, in communications between or among Mylan, Ranbaxy, and FDA, neither FDA nor Ranbaxy, despite several opportunities, has denied that Ranbaxy's ANDA is subject to the AIP.

2 Because Ranbaxy's ANDA was submitted to FDA prior to the December 8, 2003 enactment of the MMA, and because Ranbaxy's ANDA contained a certification

(D.D.C. 2000) (Judge Roberts presiding) ("*Shalala*"). Generic drugs are the same as brand-name drugs. Typically, generic drugs are sold at a lower price, resulting in cost savings to the public, including private insurers and the government (*i.e.*, through Medicaid and Medicare public payments). The Hatch-Waxman Amendments permit generic drug manufacturers to obtain FDA approval of their products so long as those products are shown to be bioequivalent to a Reference Listed Drug ("RLD") – usually an approved, branded product that FDA has already approved as safe and effective. Generic drug manufacturers accomplish this by submitting ANDAs to FDA. *See* 21 U.S.C. § 355(j); *Shalala*, 81 F. Supp. 2d at 32.

An ANDA must contain a certification or statement with respect to each patent listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") for the RLD. *See* 21 U.S.C. § 355(j)(2)(A)(vii)-(viii). ANDA sponsors may make one of four certifications with respect to each such listed patent, only one of which is relevant here – the so-called "Paragraph IV certification."[3] A Paragraph IV certification states that a listed patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of the generic drug for which the ANDA is submitted. *See id.* § 355(j)(2)(A)(vii); *Shalala*, 81 F. Supp. 2d at 33.

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to an Orange Book-listed patent for LIPITOR®, the triggering of 180-day marketing exclusivity is governed by the pre-MMA version of the statute. *See id.* § 355(j)(5)(B)(iv)(I)-(II) (2002).

[3] Alternatively, a sponsor may submit what is commonly referred to as a "section viii statement" pursuant to 21 U.S.C. § 355(j)(2)(A)(viii) for patents claiming a method of using the RLD. This alternative type of submission is not at issue here.

The Hatch-Waxman statutory scheme encourages generic drug companies to submit Paragraph IV certifications to clear the patent thicket by offering an incentive to counter the risks entailed in making such submissions. 21 U.S.C. § 355(j)(2)(A)(vii). The first ANDA sponsor to challenge a branded, Orange Book-listed patent by submitting a Paragraph IV certification usually encounters high research, development, and other costs in order to identify a legal challenge. To encourage generic drug companies to bear these costs and/or risks, the FDC Act provides an incentive for the first applicant to do so. *Id.* If its ANDA is approved, that first-to-file ANDA sponsor receives an exclusive right to market generic versions of the brand-name drug product for a period of 180 days. *Id.* Under the statutory provisions applicable here, this exclusivity period is triggered by either the first commercial marketing of the generic drug or the date of a final court decision holding that the patent is invalid, not infringed, or unenforceable. *See* 21 U.S.C. § 355(j)(5)(B)(iv)(I)-(II) (2002).

The FDC Act requires an ANDA to contain, among other things, "information to show that the new drug is bioequivalent to the listed drug" and "the items specified in clauses (B) through (F) of subsection (b)(1)." *Id.* § 355(j)(2)(A). Moreover, the ANDA must contain "a full statement of the composition of such drug" and "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug." *Id.* § 355(b)(1)(C)-(D); *see also* 21 C.F.R. § 314.50(d)(1).

Importantly, the FDC Act and the Hatch-Waxman Amendments do not authorize FDA to approve an ANDA or to confer 180-day marketing exclusivity with respect to an ANDA that contains, or is tainted by, unreliable or falsified data or information. Under

the Act's plain language, FDA cannot approve an ANDA where: (a) "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;" (b) "the application contains an untrue statement of material fact;" or (c) "the application does not meet any other requirement of [21 U.S.C. § 355(j)(2)(A)]." 21 U.S.C. § 355(j)(4).

In furtherance of its statutory mandate that ANDA submissions contain reliable data and information, FDA promulgated Compliance Policy Guide 7150.09, § 120.100, which sets forth FDA's AIP. *See* FDA Final Policy on "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities," 56 Fed. Reg. 46,191, Palmer Decl. Ex. A. The AIP states that an applicant may "subvert the integrity of an FDA review process through acts such as submitting fraudulent applications, making untrue statements of material facts, or giving or promising bribes or illegal gratuities." *Id.* at 46,199. When the FDA determines, based on

> fraudulent data in an application, that the data in the application are unreliable, the agency intends ordinarily to exercise its authority, under applicable statutes and regulations, to refuse to approve the application (in the case of a pending application) or to proceed to withdraw approval (in the case of an approved application), regardless of whether the applicant attempts to replace the unreliable data with a new submission in the form of an amendment or supplement.

*Id.* at 46,200. The AIP further states:

> [i]f the applicant wishes to replace the false data with a new submission, the new submission should be in the form of a new application. The new application should identify the parts of the original application that were found to be false.

> The truthfulness and accuracy of the new application should be certified by the president, chief executive officer, or other official most responsible for the applicant's operations.

*Id.*

Thus, regardless of whether an ANDA sponsor was "first to file," making its ANDA eligible for 180-day exclusivity, a sponsor that is subject to the AIP may not simply amend a tainted ANDA; the FDA requires a new ANDA submission and, consequently, the sponsor loses its first-to-file status. *See id.*

### C. Matrix's ANDA

Plaintiff Matrix has pending at FDA ANDA No. 91-226 for atorvastatin calcium tablets (10mg, 20mg, 40mg, and 80mg dosage strengths). Mylan is the U.S. agent for purposes of the ANDA, and following its approval, will be the commercial distributor of the product. The Matrix atorvastatin ANDA was submitted more than two years ago. Declaration of S. Wayne Talton ("Talton Decl.") ¶ 6. [redacted][4] If FDA's regulatory review of the ANDA is complete, and if no generic competitor has 180-day marketing exclusivity, Plaintiffs could launch the product on or shortly after that date.

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[4] [redacted] is the date of the expiration of pediatric exclusivity periods associated with certain patents for LIPITOR®, and thus the earliest possible date for FDA to approve [redacted] a generic atorvastatin tablet product. *Id.* ¶ 8.

### D. Atorvastatin Calcium Tablets - LIPITOR®

Pfizer branded atorvastatin calcium tablets as LIPITOR®. Approved in 1996, LIPITOR® is one of the most widely prescribed cholesterol-lowering medications worldwide. LIPITOR® is also one of the most widely prescribed drugs in the United States with over 40 million prescriptions, and with a reported $7 billion in annual sales. Palmer Decl. ¶ 10. According to IMS prescription audit data, for the 12-month period ending September 20, 2010, an estimated 2 billion doses of LIPITOR® were prescribed in the United States. Mauro Decl. ¶ 14.

As FDA states on its own website, "[g]eneric competition is associated with lower drug prices." FDA, Generic Competition and Drug Prices (Mar. 1, 2010) *available at* http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129385.htm, Palmer Decl. Ex. B. "On average, the first generic competitor on the market prices its product only slightly lower than the brand-name manufacturer," the FDA document continues. "However, the appearance of a second generic manufacturer reduces the average generic price to nearly half the brand name price." *Id.* Thus, as additional generic drug manufacturers obtain approval and launch their products, prices continue to fall, albeit more slowly. *Id.* "For products that attract a large number of generic drug manufacturers," as is believed to be the case with the generic form of LIPITOR®, "the average generic drug price falls to 20% of the branded drug price and lower." *Id.* With regard to the generic drug simvastatin, generic companies garnered 97% of the market within a year of generic launch, and the average price for the generic versions of the drug, at the end of the year, was only about 5% of the brand price. Mauro Decl. ¶ 16.

The submission of ANDAs and the contents thereof are generally kept confidential by FDA. Nevertheless, publicly available documents reveal that there are at least seven generic drug manufacturers that have submitted ANDAs for one or more strengths of atorvastatin calcium tablets. *Id.* ¶ 19.

The savings to consumers and third-party payors upon the availability of generic alternatives to LIPITOR® will be significant, and will almost certainly increase with each additional generic entrant. At the outset of generic competition for atorvastatin [redacted] if Ranbaxy does not have 180-day marketing exclusivity), there will be at least two competitors including Watson Pharmaceuticals, Inc. ("Watson"), who is the "authorized generic"[5] distributor of Pfizer's branded LIPITOR®, and Plaintiffs.[6] *Id.* ¶ 17.

The American public will benefit significantly by generic competition from Plaintiffs or others because the entry of only one generic may decrease prices only slightly, but entry of several generic competitors (*i.e.*, Mylan and the authorized generic, Watson) likely decreases prices to roughly 20 percent or lower of the price of the branded

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5 Generics that are sold pursuant to a license from the patent holder (here, Pfizer) are "authorized generics." These authorized generics are not affected by the 180-day marketing exclusivity period because they fall under the patent holder's original drug application.

6 Based on analyst reports and other publicly available information, it is believed that other generic atorvastatin competitors may be able to launch their product in the near term if Ranbaxy does not have 180-day marketing exclusivity, all of which benefits the public by increased competition and thus lower prices. However, the approval status of other generic atorvastatin ANDAs (and the timing thereof) has neither been publicly disclosed nor disclosed to Plaintiffs. *Id.* ¶ 18.

product. *See* FDA, Generic Competition and Drug Prices (Mar. 1, 2010) *available at* http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129385.htm. Palmer Decl. Ex. B.

Thus, unlawful Agency inaction that delays generic manufacturers from entering the atorvastatin generic market at the earliest legal date will deny Plaintiffs substantial revenues, and the public the substantial benefits of reduced costs for this necessary drug. FDA's inaction also potentially imposes on other generic manufacturers the loss of a significant economic opportunity.

### E. Ranbaxy's Pending Atorvastatin ANDA

Ranbaxy is a generic drug manufacturer with manufacturing locations throughout the world, including a location at Paonta Sahib, Simour District, Himachal Pradesch, India (the "Paonta Sahib site"). Based upon correspondence between Ranbaxy and FDA, it is widely believed that Ranbaxy's ANDA, submitted in August 2002, was the first ANDA submitted to FDA containing a Paragraph IV certification challenging patents listed in the Orange Book for LIPITOR®. Palmer Decl. Ex. G. As such, Ranbaxy's ANDA qualified for a period of 180-day marketing exclusivity.

The Ranbaxy ANDA at issue was submitted to FDA prior to the December 8, 2003 enactment of the MMA. Therefore, the triggering of 180-day marketing exclusivity is governed by the pre-MMA version of the statute. *See* 21 U.S.C. § 355(j)(5)(B)(iv)(I)-(II) (2002). If Ranbaxy's ANDA had been submitted *after* the effective date of the MMA, new statutory provisions governing 180-day marketing exclusivity, intended to

prevent first filers from blocking generic competition, would almost certainly have resulted in extinguishing any Ranbaxy claim to exclusivity.

### F. FDA's Long-Standing Application Integrity Policy

In a letter dated February 25, 2009, FDA advised Ranbaxy of numerous allegations of making "untrue statements of material fact" in Agency submissions and that Ranbaxy "failed to include critical information" related to stability test results and other data generated at Ranbaxy's Paonta Sahib site. *See* Letter to Mr. Malvinder Mohan Singh, Ranbaxy Laboratories, Ltd. from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, dated February 25, 2009 ("February 2009 Letter"), Palmer Decl. Ex. C. FDA's allegations implicated data for multiple pending drug applications (including at least one "pending NDA," or New Drug Application, and at least one ANDA), and stated that drug samples being held for stability testing were being stored under conditions that made "protocols and stability data submitted by Ranbaxy . . . false" (without this information being accurately reported) (*id.* at 2), that Ranbaxy testing and analysis records contained "thousands" of "errors," and that Ranbaxy failed to timely disclose a test on an unidentified drug that showed "that a specified impurity in one batch exceeded the specification limits" (more details from the letter are provided below). *Id.* at 4. FDA advised Ranbaxy in the February 2009 Letter that the Agency was invoking the AIP with respect to certain drug applications Ranbaxy submitted to FDA, but, in the publicly available version of the letter, FDA did not specify which ANDAs were implicated. *Id.*

The AIP is FDA's official statement to the industry setting forth how the Agency will respond when it discovers that drug applications submitted to the Agency contain materially false data. The AIP states that defects in a pending ANDA cannot be cured with an amendment to the ANDA setting forth or substituting untainted data. Instead, sponsors of such tainted pending ANDAs must submit new applications – and not simply amend a prior application – based on untainted data in order to obtain FDA approval. Palmer Decl. Ex. A.

In correspondence between Mylan and FDA, and between Ranbaxy and FDA, neither FDA nor Ranbaxy denies that Ranbaxy's ANDA is subject to the AIP. *See* January 5, 2011, Letter to FDA, Palmer Decl. Ex. D; January 31, 2011, Letter to FDA, Palmer Decl. Ex. E; February 22, 2011 Letter to FDA, Palmer Decl. Ex. F; February 14, 2011 Letter from Zuckerman Spaeder LLP, representing Ranbaxy, to FDA, Palmer Decl. Ex. G. Even though the Ranbaxy ANDA has been pending with FDA since August 2002, and the AIP has been invoked against Ranbaxy and the Paonta Sahib site for more than two years, FDA has failed affirmatively to disclose (a) whether the Ranbaxy ANDA is subject to the AIP, and (b) whether, if so, the Agency will enforce the AIP against Ranbaxy's ANDA and either deny the ANDA or deem it withdrawn (thus extinguishing any claim to 180-day marketing exclusivity) if it is tainted by unreliable data or other defects.

As of the date of this filing, despite repeated requests for information and/or a decision, FDA has refused to disclose any information concerning the status of Ranbaxy's ANDA. FDA has also failed or refused to disclose whether 180-day

marketing exclusivity for generic atorvastatin will apply or be extinguished. FDA's several – and repeated – failures to act directly affect Plaintiffs' rights, including but not limited to whether Plaintiffs can or will be able to commercially launch a generic version of LIPITOR® [redacted] FDA's failure to act also denies the American public the ability to purchase generic LIPITOR® at the earliest opportunity.

**G. Irreparable Harm**

FDA's failure to disclose to Plaintiffs information that is critical to Plaintiffs' ability to launch a generic version of LIPITOR® is causing Plaintiffs irreparable harm. [redacted] provided the ANDA is approved (as expected) and Plaintiffs have sufficient advance notice that Ranbaxy will not be granted 180-day marketing exclusivity.

Launching a product on the unprecedented scale of generic LIPITOR® requires months of planning, significant financial commitments and dedication of substantial other resources. It is critically important for Matrix to have begun preparations, purchases, adjustments to production schedules, validation and manufacturing now if the company intends to capture the substantial benefits related to being among the first to enter the market for generic LIPITOR®. Babu Decl. ¶¶ 8, 12.

Matrix conservatively anticipates that, upon commencement of generic competition for LIPITOR®, it will be able to supply a 20% share of the LIPITOR®

generic market described above, which requires manufacture of hundreds of millions of doses in the first year after launch. *Id.* ¶¶ 12-14. [7] Matrix must complete the manufacture and production of more than 100 million dosage units by approximately June 20, 2011, so that those doses will be available for a commercial launch as early as June 28, 2011. *Id.* Producing more than 100 million dosage units for a projected launch date of as early as June 28 requires significant production efforts, including (1) millions of dollars in inventory expenditures, (2) millions of dollars in additional capital expenditures, (3) running manufacturing equipment beyond utilization capacity, and (4) displacement of several other products during the manufacturing and production process, among other things. These efforts, combined with capital expenditures necessary to increase Matrix's current manufacturing capacity to meet projected demand, will cost Matrix tens of millions of dollars between now and the end of June, 2011, not including the incalculable loss of revenues for products that Matrix cannot manufacture because it diverted manufacturing capacity from other products to atorvastatin. *Id.* ¶¶ 12-22.

Therefore, in order for Matrix to timely launch generic LIPITOR®, and provide the public access to generic LIPITOR® as soon as possible, Plaintiffs need to know immediately whether the Ranbaxy ANDA will be denied 180-day marketing exclusivity.

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[7] The projected amounts of atorvastatin required to meet demand, and the costs per unit to produce that atorvastatin, are highly confidential business information, so precise numbers for costs of production will be included in a Declaration to be filed separately as an attachment to a Motion to Seal. The precise numbers will not be repeated here, so that a publicly available version of this Memorandum will not need to be redacted.

In the absence of such certainty, and if FDA only late in the game determines that no atorvastatin ANDA sponsor will be granted 180-day marketing exclusivity, Plaintiffs will be irreparably harmed by, among other things, not having sufficient product to supply the market, thus incurring a significant loss of revenue and loss of customer goodwill. *Id.* ¶¶ 25, 26. If Matrix continues preparations to manufacture generic LIPITOR® (as described above), then later learns that Ranbaxy's ANDA is somehow approved, and FDA grants 180-day marketing exclusivity to Ranbaxy, Matrix will have wasted valuable resources manufacturing drug products that it will not be able to sell. *Id.* ¶ 24. This is because atorvastatin has a shelf life of 18 months, and wholesalers generally will not purchase prescription drugs that are labeled with expiration dates 18 months after manufacture if, at the time of sale, the products have less than 12 months of shelf life remaining. *Id.* In addition, Matrix will have diverted its resources away from manufacturing and selling other important drug products. *Id.* ¶ 19.

Therefore, the uncertainty that FDA's inaction has created has already caused irreparable harm, and threatens further massive losses for Plaintiffs either way. *Id.* ¶¶ 24, 25. If Matrix manufactures atorvastatin with an expectation of launch [redacted] and then is unable to launch until 180 days after Ranbaxy begins marketing its product (which could be years from now), Plaintiffs' product will go unsold. If Matrix does not manufacture sufficient product, and it turns out that its ANDA is approved for launch [redacted] Plaintiffs will never recover the lost resources, time, sales, and their effect on revenue. *Id.* ¶ 26. Indeed, if FDA had made a timely decision on Ranbaxy's eligibility for 180-day marketing exclusivity two months ago, when it learned

that at least one generic applicant (Matrix) [redacted] Matrix would have geared up for production sufficient to meet a greater share of the generic market. *Id.* ¶ 14. In other words, irreparable harm to Matrix, and to Mylan, has already occurred because of FDA's inaction, due to lost sales opportunities. Mauro Decl. ¶ 20. Lastly, the public interest has been and will be immensely and irreparably harmed by, among other causes, the public's inability to procure at the earliest possible time sufficient quantities of one of the most widely prescribed drugs in the United States at significantly lower generic drug prices.

As the foregoing reflects, FDA's position with respect to the Ranbaxy ANDA directly affects business decisions that Plaintiffs must make now. The existence or non-existence of a period of 180-day marketing exclusivity will dictate when and how much product needs to be manufactured and shipped, and an orderly market for generic LIPITOR® cannot be established without an FDA decision well before June 28, 2011.

## III. LEGAL ARGUMENT

### A. Standard of Review for Issuance of a Preliminary Injunction

The legal standard for a preliminary injunction is well established in the D.C. Circuit:

> When deciding whether to grant a preliminary injunction, a district court must consider four familiar factors: whether "(1) the plaintiff has a substantial likelihood of success on the merits; (2) the plaintiff would suffer irreparable injury were an injunction not granted; (3) an injunction would substantially injure other interested parties; and (4) the grant of an injunction would further the public interest."

*Sottera, Inc. v. FDA*, 627 F.3d 891, 893 (D.C. Cir. 2010), quoting *Arkansas Dairy Coop. Ass'n v. U.S. Dep't of Agric.*, 573 F.3d 815, 821 (D.C. Cir. 2009); *see also Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 2009); *CityFed Fin. Corp. v. Office of Thrift Supervision*, 58 F.3d 738, 746 (D.C. Cir. 1995). "In deciding whether to grant an injunction, the district court must balance the strengths of the requesting party's arguments in each of the four required areas. If the arguments for one factor are particularly strong, an injunction may issue even if the arguments in other areas are rather weak." *CityFed*, 58 F.3d at 747; *see also Sataki v. Broadcasting Bd. of Governors*, 733 F. Supp. 2d 22, 44 (D.D.C. 2010); *Shalala*, 81 F. Supp. 2d at 36. Notwithstanding this flexibility, the movant must show "at least some likelihood of irreparable harm in the absence of an injunction" and "a substantial likelihood of success on the merits." *Sataki*, 733 F. Supp. 2d at 44. As described below, review of the four statutory factors here tips decisively in favor of granting Plaintiffs' requested injunctive relief.

### B. Plaintiffs Are Likely to Succeed on the Merits of Their Claim That FDA's Failure to Decide Whether to Reject Ranbaxy's ANDA and Whether Ranbaxy Has 180-Day Marketing Exclusivity Is Unlawful, Unreasonable, Arbitrary, and Capricious

#### 1. Applicable Law, Regulations and the AIP Require FDA To Make a Decision Now Concerning the Ranbaxy Atorvastatin ANDA

The applicable law, regulations, and FDA's long-established policies require FDA to make a decision now whether the Ranbaxy ANDA is eligible for 180-day marketing exclusivity. First, under the plain language of the FDC Act, FDA is ***not*** authorized to

approve an ANDA where: (a) "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;" (b) "the application contains an untrue statement of material fact;" or (c) "the application does not meet any other requirement of [21 U.S.C. § 355(j)(2)(A)]." 21 U.S.C. § 355(j)(4); *see also* 21 C.F.R. § 314.127(a).

Second, FDA's official policy statement regarding how the Agency will address ANDA submissions where the FDA learns that the ANDA contains, or is otherwise based on, false material information requires FDA to take action to address applications affected by the findings described in FDA's February 2009 letter. The AIP provides, in relevant part:

> When FDA finds, based on fraudulent data in an application, that the data in the application are unreliable, the agency intends ordinarily to exercise its authority, under applicable statutes and regulations, to refuse to approve the application (in the case of a pending application) or to proceed to withdraw approval (in the case of an approved application), regardless of whether the applicant attempts to replace the unreliable data with a new submission in the form of an amendment or supplement. Thus, if the applicant wishes to replace the false data with a new submission, the new submission should be in the form of a new application. The new application should identify the parts of the original application that were found to be false. The truthfulness and accuracy of the new application should be certified by the president, chief executive officer, or other official most responsible for the applicant's operations.

Palmer Decl. Ex. A. FDA has publicly stated that Ranbaxy has shown a "pattern and practice of submitting untrue statements of material fact and other wrongful conduct, which raise significant questions regarding the reliability of the data and information

contained in applications (pending and approved)" that Ranbaxy submitted to the Agency.[8] While only FDA and Ranbaxy know for certain if the atorvastatin ANDA is covered by the AIP, FDA's invocation of the sanction set forth in the AIP – "to refuse to approve the application" – would be appropriate for any ANDA covered by the policy. *See id.*

If the conditions FDA discussed in its February 2009 Letter about the Paonta Sahib site apply to Ranbaxy's ANDA, Plaintiffs have reason to believe that FDA should deny the Ranbaxy ANDA. FDA's February 2009 Letter contains a litany of findings with respect to stability test results and other "untrue statements of material fact" that Ranbaxy submitted to FDA in the company's ANDAs. FDA's findings detailed in the February 2009 letter include, but are not limited to, the following:

- Ranbaxy "submitted untrue statements of material fact in abbreviated and new drug applications." *Id.* at 1.

- "Ranbaxy submitted stability information in numerous approved and pending applications that contain untrue statements of material fact, because Ranbaxy failed to include critical information about the storage and testing of the product." The Agency found that Ranbaxy had improperly stored "hundreds of stability samples" in refrigerators (when many of the samples were being tested for room temperature or accelerated studies).[9] However, Ranbaxy's "sample logbooks did

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[8] *See* February 2009 Letter at 5, Palmer Decl. Ex. C.

[9] Storage of stability samples in a refrigerator, when they were supposed to be stored either at room temperature or at higher temperatures necessary for accelerated stability studies, would render the data unreliable, since most drug products degrade much faster at higher temperatures than at lower temperatures, as indicated in FDA's Guidance for Industry - Q1A(R2) Stability Testing of New Drug Substances and Products (Nov. 2003) *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073369.pdf (accelerated study conditions defined at page 20 as being designed "to increase the rate of chemical degradation or physical change of

not identify the samples that were being held in the refrigerators, their storage duration in the refrigerators, and the justification of this storage." *Id.*

- Ranbaxy's "unusual storage condition for stability testing was not defined in the submitted protocol for U.S. drug applications, and prior to the February 2006 inspection, was not reported to FDA." *Id.* at 2.

- A Ranbaxy audit of stability data in an unidentified number of "pending ANDAs found 2257 errors in entries for the dates of analysis." FDA also found "errors in 1385 entries for stability test results." *Id.* at 3.

- "These submissions of false information about the stability testing of the product were material to FDA's review of these applications." *Id.*

Unless Ranbaxy can establish that these conditions did not apply to its atorvastatin ANDA, we do not know how Ranbaxy would be able to demonstrate that the data for the company's atorvastatin samples were "reliable," except by submitting new data, which, under the AIP, requires the submission of a new ANDA (extinguishing any claim to 180-day marketing exclusivity). Palmer Decl. Ex. C at 6, Ex. A. We note that FDA issued the February 2009 Letter imposing the AIP on the Paonta Sahib site after Ranbaxy had previously provided FDA in July 2007 a report on its "stability verification project." Palmer Decl. Ex. C at 2. Nonetheless, as stated in the AIP and the February 2009 Letter, FDA found indications of "a pattern and practice of submitting untrue statements of material fact and other wrongful conduct, which raise significant questions regarding the

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a drug substance," and accelerated conditions for drug products not labeled for refrigeration require elevated temperatures, generally, with temperatures at about 40 degrees Celsius (or about 104 degrees Fahrenheit)). Palmer Decl. Ex. H. Such storage conditions likely would artificially and unrealistically indicate that the product remained within specifications (including meeting specifications for potency) far longer than would truly be the case.

reliability of the data and information contained in applications . . . filed with the Agency and which contain data developed at the . . . Paonta Sahib site." *Id.* at 5.

Plaintiffs are not aware of any past instances where FDA has invoked the AIP and then approved an ANDA when the data supporting the application were false, unreliable and/or tainted by misconduct. Plaintiffs are also unaware of any past instances where the FDA has invoked the AIP against the sponsor of a pending ANDA for reasons similar to those set forth in the February 2009 Letter, and then permitted that ANDA sponsor to "cure" the tainted application by an amendment. In light of this history, it is impermissible for FDA to refuse to disclose whether the Ranbaxy ANDA for atorvastatin is covered by the AIP, and, if so, whether FDA will reject that application.

Third, FDA's implementing regulations demonstrate that FDA must take appropriate action in this case, again, assuming that the Ranbaxy ANDA is covered by the AIP. The FDA may consider an ANDA sponsor's failure to take certain actions with respect to its pending ANDA "to be a request by the applicant to withdraw the application." 21 C.F.R. § 314.110(c)(1). While the provisions of that regulatory section apply specifically to situations where an ANDA sponsor has received a "complete response letter" (which is not the case here), the regulations demonstrate that, pursuant to the FDC Act, FDA has the authority to deem an application to be withdrawn under appropriate circumstances.

Fourth, FDA possesses *inherent* authority to make decisions concerning the status of the Ranbaxy ANDA, especially where the rights of Plaintiffs and the public are so deeply affected by FDA's refusal to make a decision. FDA's "inherent" authority has

been the subject of litigation involving ANDAs tainted by the type of unreliable data described in the February 2009 Letter. In *American Therapeutics v. Sullivan*, 755 F. Supp. 1 (D.D.C. 1990), FDA withdrew approval of an ANDA because the Agency concluded that the approval was a mistake. The plaintiff argued that FDA had no authority to withdraw the approval because FDA had not followed the statutorily mandated procedures in Section 505 of the FDC Act for withdrawing ANDA approvals. The Court disagreed, and observed that even without following those procedures, courts defer to FDA so that the Agency can remedy "mistakes" even though there was no explicit language in the FDC Act that authorized FDA's actions. *Id.*[10]

Based on all of the foregoing, the FDC Act, and FDA's own policies, FDA is required to make a determination now concerning whether to grant or deny Ranbaxy 180-day marketing exclusivity in connection with its atorvastatin ANDA. FDA's arbitrary failure to disclose whether the Ranbaxy ANDA is subject to AIP, and, if so, whether the Agency will enforce the AIP or otherwise deny Ranbaxy 180-day marketing exclusivity is causing significant uncertainty and likely delay in opening the market for generic atorvastatin, all of which causes and will continue to cause Plaintiffs irreparable harm and detriment to the public health.

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[10] *See also Boesche v. Udall*, 373 U.S. 472, 476-79 (1963) (the overall language of the statute and its legislative history did not affect the government's "traditional administrative authority" to do what the statute did not on its face specifically authorize); *Gun South, Inc. v. Brady*, 877 F.2d 858, 862 (11th Cir. 1989) (implied authority to rectify errors).

### 2. Agency Action Is Arbitrary and Capricious Where It Deviates from Established Policy or Precedent Without Adequate Explanation

Faced with the above facts and legal precedent, the Administrative Procedure Act ("APA") requires FDA to make a decision in this case. Under the APA, "the reviewing court shall . . . compel agency action unlawfully withheld or unreasonably delayed; and . . . hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706. "Agency action" includes an agency's delay or failure to act. *Id.* §§ 551(13), 701(b)(2).

In this case FDA refuses to disclose, despite repeated requests, whether the AIP applies to Ranbaxy's ANDA, and, if so, whether FDA will enforce the AIP, and deny Ranbaxy's 180-day marketing exclusivity. Although courts are deferential to agencies acting within their zone of expertise, the D.C. Circuit has held that such discretion is not unfettered: It does not permit an agency to persist in conduct that produces a result hostile to clear statutory intent. *See Teva Pharm. USA, Inc. v. Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010). This principle applies to Congress' statutory mandate that FDA approve an ANDA unless, among other things, it contains inaccurate or false data. *See* 21 U.S.C. § 355(j)(4). FDA has all the information it needs to act now. FDA's impermissible inaction causes irreparable harm to Plaintiffs and unlawfully precludes or delays the opening of the generic LIPITOR® market, in contravention of the letter and intent of the Hatch-Waxman Amendments to promote the availability of affordable generic alternatives to brand-name drugs.

### C. Plaintiffs Will Suffer Irreparable Harm If FDA Further Delays a Decision on Ranbaxy's ANDA

FDA's continued delay in applying its well-established AIP policy (or in the alternative, informing the market that Ranbaxy's ANDA is not subject to the AIP) effectively precludes Plaintiffs and other generic participants from entering the market for the world's most prescribed drug product at the earliest possible date.

This Court has acknowledged that "the earliest generic drug manufacturer in a specific market has a distinct advantage over later entrants," and that being falsely denied the right to be the earliest generic manufacturer constitutes irreparable harm. *See Mova Pharm. Corp. v. Shalala*, 955 F. Supp. 128 (D.D.C. 1997). A manufacturer that is prevented from entering the market at the earliest possible date, because a competitor has wrongfully captured the 180-day marketing exclusivity or early market entry, is at a distinct disadvantage. *See id.*

In the present case, subject to FDA regulatory approval, [redacted] FDA's failure to make a decision on Ranbaxy's ANDA indefinitely and purposelessly delays Plaintiffs' commercial launch and the opening of the generic market for atorvastatin. Such inaction and delay deny Plaintiffs and other generic manufacturers the significant economic benefits of entering the market; deny the public access to high-quality, less expensive generic alternatives to LIPITOR® at the earliest possible date; and deny the government as a public payor through its Medicare and Medicaid programs access to less expensive, generic versions of the country's popular, widely prescribed brand-name drug product.

All of this results in a loss of significant savings to the American public in the amount of approximately $3.9 billion annually, or a daily savings of $10.9 million. Mauro Decl. ¶¶ 15-16. It amounts to an estimated loss in savings to the federal government (as a payor for Medicare Part D, Medicaid and Veterans' benefits) of $1.3 billion annually, or $3.8 million per day. *Id.* If generic manufacturers capture more than 95% of the market in the first year after launch, like that of at least one other cholesterol-lowering product (*i.e.*, simvastatin), the public stands to save billions more. Savings could be as high as $6.7 billion annually (or $18.3 million per day) for all Americans, or as high as $2.3 billion annually (or $6.4 million per day) for the government as a payor. *Id.*

Even a temporary, further delay by FDA in discharging the Agency's obligation to disclose the status of Ranbaxy's ANDA, including whether Ranbaxy will maintain its 180-day marketing exclusivity, will cause significant harm to Plaintiffs.

If, for example, Plaintiffs can commence marketing of the drug in [redacted] then they must continue making preparations now. A significant lead-time is necessary before marketing operations begin to permit sufficient time to comply with numerous premarketing requirements. As stated above, it is critically important for Matrix to have begun preparations, purchases, adjustments to production schedules, validation and manufacturing now in order for the company to capture the substantial benefits related to being among the first to enter the market for generic LIPITOR®. Babu Decl. ¶¶ 8-12. Matrix has begun manufacturing Active Pharmaceutical Ingredient ("API") on a commercial scale that exceeds the current capacity of the company's current manufacturing equipment. *Id.* ¶¶ 18-20. [redacted]

[redacted] Matrix must make millions of dollars in capital expenditures both in terms of production of API and finished dosage forms of the product. *Id.* ¶¶ 15-19. Matrix will also have to divert production of other important products and displace other products in the production and manufacturing queue in order to be able to make the projected atorvastatin finished doses, at an incalculable cost to Matrix. *Id.* ¶¶ 15-23. Matrix will also have to increase inventory replenishment levels in order to meet projected demand, which costs Matrix millions of dollars. *Id.* The costs associated with the manufacture of atorvastatin alone (not including consequential revenue losses from lost sales of displaced products) amount to millions of dollars. *Id.* ¶ 22.

If, alternatively, Matrix and Mylan do not prepare for launch and FDA denies 180-day marketing exclusivity to Ranbaxy, Mylan has already lost and will lose substantially more revenue as one of the first competitors – if not the only generic competitor – to the brand LIPITOR®. Mauro Decl. ¶ 20. This loss of revenue would amount to a significant percentage of Mylan's revenue in the United States in the first year after launch.[11] *See id.* ¶¶ 4, 20. Then, if Mylan is suddenly faced with unexpected entry into the atorvastatin market, the ramping up of manufacturing of API and finished product, the displacement of other production, and all the other repercussions will have to occur in a compressed period of time in order to reach market as soon as possible. Babu Decl. ¶¶ 15-23.

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[11] The amount of projected revenue, and the total United States revenues for Mylan, are confidential business information that will not be repeated here, so that a publicly available version of this Memorandum will not need to be redacted.

[redacted]

FDA's failure to act – one way or the other – on Ranbaxy's ANDA puts Plaintiffs between a rock and a hard place. On the one hand, if the AIP is applicable and FDA further delays enforcing the AIP or otherwise rejecting Ranbaxy's ANDA, Plaintiffs will be irreparably harmed by being denied the time to adequately prepare to enter the market at the earliest date, and by suffering the loss of revenue and economic opportunity caused by being late to market. Babu Decl. ¶¶ 23-27; Mauro Decl. ¶ 20. The public also loses the benefit of access to a generic atorvastatin product that would be priced much lower than LIPITOR®. On the other hand, if Plaintiffs proceed in anticipation of FDA's eventual rejection of Ranbaxy's ANDA, and FDA determines Ranbaxy is eligible for 180-day marketing exclusivity, then Plaintiffs will have irretrievably wasted tremendous resources of tens of millions of dollars preparing to launch a product that can neither be sold nor retained until sales are permitted. Babu Decl. ¶ 22. Plaintiffs also will have lost out on sales of products Plaintiffs would have manufactured, but had to displace to manufacture atorvastatin. *Id.* ¶ 25. In either case, FDA's silence denies Plaintiffs the ability to make rational business plans, and forces Plaintiffs to choose between which harm they are less willing to risk. Thus, absent this Court's action, Plaintiffs will suffer irreparable harm.

This Court's prior decision in *Shalala*, finding inadequate proof of irreparable harm, is not relevant to the circumstances presented here. The Court there found that loss

of revenue amounted to only about 0.4% of annual revenue, whereas, with atorvastatin, preventing Mylan from reaching market for a year has resulted or would result in loss of a very significant percentage of its annual United States revenue.[12] The Court there also found that Mylan had unreasonably delayed bringing its Motion for Preliminary Injunction, which "undercuts its allegation of irreparable harm." *Shalala*, 81 F. Supp. 2d at 43. [redacted] Two months of effort to secure agency action before filing a lawsuit to compel agency action is not an unwarranted delay.

### D. The Public Interest Benefits If the Court Requires FDA to Make a Decision on the Status of Ranbaxy's ANDA

Consideration of the public interest tips decisively in favor of an injunction because FDA's decision – one way or another – concerning Ranbaxy's eligibility for 180-day marketing exclusivity significantly benefits the public interest. FDA faces two options with respect to the Ranbaxy ANDA, and the Agency possesses all of the information necessary to make a decision now. Either outcome benefits the public interest. If FDA makes a decision *denying* Ranbaxy 180-day marketing exclusivity or

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12 The percentage of projected annual revenue that atorvastatin sales would generate is highly confidential business information. The number is included in the unredacted Mauro Dec. at ¶ 20 that is attached to a Motion to Seal filed contemporaneously with this Memorandum.

rejecting the ANDA outright, then the public likely will have access lower-cost generic alternatives to LIPITOR® at the earliest possible date. If, however, FDA makes a decision acknowledging Ranbaxy eligibility for 180-day marketing exclusivity or approves Ranbaxy's atorvastatin ANDA, then at least Plaintiffs and other market participants will be able to make critical financial, resource allocation, marketing, and other decisions soon. By contrast, if FDA *fails to decide* now whether Ranbaxy is eligible for 180-day marketing exclusivity, then it is uncertain when the public will reap the benefits of access to a generic form of LIPITOR®. Plaintiffs are left with significant financial and other uncertainty concerning when and how to launch a generic atorvastatin product.

FDA's failure to clarify the rights of Plaintiffs and other generic drug manufacturers *vis-a-vis* the Ranbaxy ANDA denies them the certainty necessary to make business plans and appropriate manufacturing decisions. When generic competitors are placed in this position, generic competition that will save the public and government healthcare systems millions of dollars a day and billions of dollars a year is lost, and it can never be recovered.

### E. Other Interested Parties Will Not be Injured by the Issuance of the Requested Injunction Pending a Full Hearing on the Merits

Review of an application for a preliminary injunction also requires the Court to consider whether the adverse party will be injured by imposition of an injunction. This factor also favors issuance of the injunction sought by Plaintiffs.

FDA cannot claim to have a stake in whether Ranbaxy's ANDA is rejected or not, other than the Agency's duty to provide the public with access, as soon as possible, to safe and effective generic versions of widely used drugs, which favors issuance of the relief Plaintiffs seek. Likewise, Ranbaxy cannot claim to be injured by an expedited decision on whether or not its ANDA is eligible for 180-day marketing exclusivity.

## IV. CONCLUSION

For all of the foregoing reasons, Plaintiffs respectfully request this Court to grant their request for a preliminary injunction enjoining FDA from continuing to deviate from the law and established Agency policy, and to require FDA to decide now whether Ranbaxy's ANDA is eligible for 180-day marketing exclusivity for its generic atorvastatin ANDA.

Dated: March 24, 2011

Respectfully submitted,

MYLAN PHARMACEUTICALS INC. and
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