October 22, 2007

VIA HAND-DELIVERY

Dockets Management Branch
Food and Drug Administration,
HFA - 305
Room 1061
5630 Fishers Lane
Rockville, MD 20857

Re: Docket No. 2007N-0382; Comments Regarding Exclusivity for Ramipril

Ranbaxy Inc. submits these comments regarding 180-day exclusivity for ramipril capsules associated with U.S. Patent No. 5,061,722 (the '722 patent). Ranbaxy's views on 180-day exclusivity[1] are as follows:

1. Cobalt Pharmaceuticals, Inc. (Cobalt) has not forfeited its statutory entitlement to 180-day exclusivity.
2. Lupin Pharmaceuticals, Inc. (Lupin) should not be permitted to withdraw its paragraph IV certification.
3. Cobalt's 180-day exclusivity period will not be triggered by the filing of a tentative decision by the court of appeals.

I. Cobalt Has Not Forfeited Its Exclusivity.

Comments submitted to the docket argue that Cobalt has forfeited its statutory entitlement to exclusivity by effectively converting its paragraph IV certification into a paragraph III certification. According to the comments, this conversion occurred because (1) Cobalt conceded in an infringement suit brought by the patent holder that its ANDA products would infringe the patent, (2) Cobalt settled the infringement suit without resolution of Cobalt's position that the patent is invalid, and (3) Cobalt is marketing an authorized generic and is not marketing its approved ramipril product.

The agency should reject these arguments because (1) the agency has no authority to require a paragraph IV applicant to commit to launching its product or to litigating its patent position prior to patent expiration and (2) the agency has not developed a record that would support an adjudication of Cobalt's intent to launch.

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[1] Because the determination of 180-day exclusivity must be based on the statutory provisions in effect prior to passage of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), some reference to the Food, Drug, and Cosmetic Act (FDCA) are to the provisions in effect prior to enactment of the MMA, and are identified herein as "Pre-MMA."

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A. A Paragraph IV Certification Is Not a Commitment to Launch a Product.

1. The Plain Meaning of the Statute.

The statute is clear with regard to patent certifications. An applicant submitting a 505(b)(2) NDA or ANDA must file one four certifications for any patent claiming the reference (or "listed") drug (composition, formulation, or active ingredient).[2] In the case of a paragraph IV certification, the statute requires a certification "that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted."[3] In the case of a paragraph III certification, the statute requires only a certification "of the date on which such patent will expire."[4] These certifications are specific and limited, and the statute reinforces this point by providing immediately below the ANDA certification provisions that "[t]he Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)" (which include the certification provisions in clause vii).

A requirement that an applicant submitting a 505(b)(2) NDA or ANDA certify that the patent is invalid or not infringed is, by its plain meaning, a certification as to the applicant's position on a legal question: whether the patent is invalid or would be infringed by the 505(b)(2) NDA or ANDA applicant's product. It is not a certification of the applicant's intent to launch its product prior to expiration of the patent or within any other given timeframe. It is not, in fact, a certification that the applicant will launch its product at all. Under the rule of *Chevron,* this plain meaning of the statute must govern.[5]

2. The Purpose of a Patent Certification.

Even if the wording of the statute were ambiguous – which is not the case – the agency would have no reasonable basis for interpreting a certification requirement regarding the scope and validity of a patent as a certification requirement regarding the specific nature and certainty of the applicant's marketing strategy. An applicant submitting a 505(b)(2) NDA or ANDA may choose to challenge the scope or validity of a patent without having decided whether it will market its product prior to expiration of the patent – or at all. The applicant may contemplate selling its NDA or ANDA, selectively waiving its 180-day exclusivity (in the case of an ANDA) in return for compensation, or considering other business strategies that may leave the launch or anticipated date of launch uncertain. There is nothing in the statute to suggest that Congress intended to require an applicant submitting a 505(b)(2) NDA or ANDA to certify to a business strategy that would satisfy an administrative agency as to the certainty or timing of launch of the applicant's NDA or ANDA product.

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2 FDCA §§ 505(b)(2)(A), (j)(2)(A)(vii).

3 FDCA §§ 505(b)(2)(A)(iv), (j)(2)(A)(vii)(IV).

4 FDCA §§ 505(b)(2)(A)(iii), (j)(2)(A)(vii)(III).

5 *Chevron U.S.A., Inc., v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-43 (1984).

The patent certification provision is, purely and simply, a provision to enable applicants submitting 505(b)(2) NDAs and ANDAs to resolve patent issues prior to approval of their products. Its purpose is to provide notice to FDA regarding eligibility for approval prior to patent expiration, and to trigger a requirement that the applicant provide a notice to the patent owner of the basis for the applicant's position on the patent.[6] Its purpose is clearly not, as suggested by comments submitted to this docket, to preclude a 505(b)(2) or ANDA applicant from challenging a patent if the applicant is unable to commit to launching its product during the term of the patent.

As noted above, an applicant submitting a 505(b)(2) NDA or ANDA might be unable to commit with certainty to launching its product, or to launching within a certain timeframe, because the applicant is considering selling its application, selectively waiving its 180-day exclusivity (in the case of an ANDA) to another applicant, or engaging in other business strategies that might impede or delay launch of its product. The applicant might also simply be uncertain whether it will be able to overcome commercial or regulatory hurdles that might delay launch of its product.

Moreover, FDA's longstanding policies directly contravene the notion that a paragraph IV certification requires a commitment to launch the applicant's product prior to expiration of the patent. FDA permits transfers of 505(b)(2) NDAs and ANDAs to new applicants and selective waivers of 180-day exclusivity by applicants that are unable to launch their products without requiring those applicants to forfeit their exclusivity. The agency also imposes statutory delays on effective approval of exclusivity-protected ANDAs that extend beyond the expiration of patent without requiring forfeiture of the exclusivity. These policies and precedents cannot be squared with the notion that a paragraph IV certification cannot be filed or maintained in the absence of a commitment to launch prior to patent expiration.

The 180-day exclusivity provisions of the statute do not amend or vitiate the straightforward paragraph IV certification provision of the statute. While the paragraph IV certification plays a role in the 180-day exclusivity scheme, its role is simply to define the class of applications that are subject to the exclusivity provisions.

In sum, there is nothing in the statute to suggest that the clear and simple statutory requirement for paragraph IV applicants certify that the patent is invalid or not infringed contains or entails a commitment to launch a 505(b)(2) NDA or ANDA product within a given timeframe. It is clear, moreover, that FDA has demonstrated through its policies

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[6] Although the notice provision of the statute requires that the notice state that "the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent" (FDCA § (j)(2)(B)(ii) (Pre-MMA)), it is clear that the patent holder is being put on notice that certification is intended to secure an effective approval (one that will permit marketing) prior to expiration of the patent, as distinct from a paragraph III certification that will permit a only a tentative approval prior to expiration of the patent. The statute requires a description of the nature and effect of the certification rather than a description of a commitment by the applicant to market its product within a given timeframe.

and actions that a paragraph IV applicant's failure or inability to commit to launch prior to patent expiration does not result in forfeiture of exclusivity.

B. A Paragraph IV Certification Is Not a Commitment to Litigate a Patent Position.

Comments submitted to this docket suggest that a paragraph IV certification is a commitment to litigate an infringement suit to fruition once such a suit has been filed. As described above, however, a paragraph IV certification is, by its plain meaning, a statement of the applicant's legal position. The statute does not require a statement with regard to intent to defend an infringement suit and, in the case of an ANDA, directs that FDA not require any certification beyond the applicant's position on validity and infringement.

Moreover, even if the statute were ambiguous regarding the substance of a paragraph IV certification – which is not the case – there is nothing in the statute to suggest that a statement regarding validity or infringement should be deemed a commitment to litigate an infringement suit in a certain manner – or to litigate at all.

Comments submitted to this docket point to Cobalt's stipulation that its ANDA product infringed the '722 patent and argue that the stipulation effected a change in its certification. This is demonstrably incorrect because Cobalt certified invalidity as well as non-infringement, and the settlement of the infringement suit preserved Cobalt's position on invalidity. The settlement reserved the issue of validity by stipulating to dismissing without prejudice and requiring that notice be provided to the patent holder prior to launch of the ANDA product by Cobalt or an assign. This notice would permit an infringement action at which Cobalt or its assign could contest invalidity.

Of course, were a paragraph IV applicant to stipulate in an infringement suit that the patent is valid *and* infringed, that statement would undermine a certification to the opposite effect and might be deemed to effect a change in the certification. A stipulation that permits the applicant to maintain its position that the patent as either invalid or not infringed, however, is not inconsistent with a paragraph IV certification and cannot be deemed to effect a change in the certification, regardless whether applicant convinces the patent holder to settle a pending infringement suit – or to delay the filing of infringement suit – or to refrain from bringing such a suit. The purpose of a paragraph IV certification is not to require adversity or litigation. It is to make the applicant's patent position known to FDA and to the patent holder.

C. "Intent to Launch" Is Not an Appropriate or Workable Standard.

Even if Congress' intent regarding the patent certification provisions were ambiguous – which is not the case – FDA's imposition of a certification of intent to launch would be unreasonable. The agency would have to define what constitutes "intent to launch" prior to expiration of a patent. Among the questions to be answered would be the following:

- Is "intent" a function of desire, interest, certainty, or formal commitment?
- What if the applicant has not determined whether or not it will launch prior to expiration?
- How certain must the applicant be that its plans will not change?
- What if the applicant would like to launch prior to expiration but is uncertain of its ability to do so?
- How certain must the applicant be of its ability to launch?
- Would the applicant be required to commit formally to launch prior to expiration?
- If a paragraph IV certification is amended due to uncertainty or changed expectations concerning launch, and amended again once the uncertainties or expectations are removed, would the applicant still qualify for exclusivity?
- What if the applicant is unable to launch, or is uncertain of its ability to launch, because of impediments in FDA's approval process?
- Would a negotiation over transfer of an ANDA or to waive exclusivity disqualify an applicant from exclusivity?
- Would the actual transfer of the ANDA or waiver of exclusivity disqualify the applicant from exclusivity?

It is unclear what definition of "intent" the agency could impose (other than a simple, absolute, and enduring commitment to launch) that would be clear and discernable to a generic drug company. The effect of an ambiguous standard, however, is quite clear and discernable. The generic drug market is a commodity market. Generic drug companies battle constant uncertainty and thrive on flexibility to consider and enter into new business arrangements at the drop of a hat. It is unclear how a 505(b)(2) or ANDA applicant company would be able to judge, much less how FDA would be able to judge, whether, on any given day, the applicant company "intended" to launch a specific product within a set timeframe.

Because Congress did not intend or even contemplate an intent-to-launch criterion as part of a paragraph IV certification, there is no guidance in the statute or legislative history. Nor is there any guidance to be had from any analogous statute other source that has been cited by FDA or by comments submitted to this docket. The lack of a clear and discernable standard for measuring "intent to launch" would violate due process and, on a practical level, would harm the industry's ability to engage in business planning based on 180-day exclusivity. It would also impair the flexibility of the industry to modify business plans based on unforeseen difficulties or opportunities in the marketplace.

Beyond the inherent ambiguity of such a standard, it is inappropriate for FDA to impose qualification for 180-day exclusivity that would require continuous public disclosure of an applicant's confidential business plans, difficulties, and uncertainties. This sort of confidential commercial information is the lifeblood of a generic drug company and is generally protected by statute and regulation. It is also inappropriate for the agency to review and pass judgment on a company's business plans, whether based on public or confidential submissions. The Hatch-Waxman Amendments were not

intended as a general authorization for FDA to regulate marketing intentions, and there is no reasonable standard derived from the statute to support the call for FDA to embark on such a regulatory adventure.

The imposition of an intent-to-launch standard, without clear parameters and requiring an administrative inquisition into an applicant's business plans, would also be contrary to the purpose of the 180-day exclusivity provision to provide an incentive to challenge patents (a purpose espoused by FDA as well as the comments in this docket). The imposition of an exclusivity forfeiture standard based on a 505(b)(2) or ANDA applicant's potential inability or unwillingness to commit to marketing its product by a date certain, to forego consideration of transfer of its application or other business options that might present themselves, and to disclose its business plans to the public or to the agency would clearly undermine the applicant's incentive to challenge the patent.

D. The Factual Allegations in this Docket Do Not Establish "Intent."

The factual allegations in this docket illustrate the inherent problems in the proposed "intent-to-launch" standard. Comments submitted to this docket suggest that FDA can determine Cobalt's "intent" based on settlement of the infringement suit, Cobalt's failure to launch its product upon approval of its ANDA, and Cobalt's failure to announce publicly that it intends to launch its ANDA product.

Here are three logical truths:

1. The settlement of the infringement suit does not establish Cobalt's intent to launch or to refrain from launching its product. The settlement leaves Cobalt free to launch after providing the patent holder with notice.

2. Cobalt's marketing of an authorized generic rather than its ANDA product does not establish an intent to launch or to refrain from launching Cobalt's ANDA product prior to expiration of the patent. Cobalt is free to launch its ANDA product based on a business plan that is unknowable to FDA or to parties submitting comments to this docket unless disclosed to them by Cobalt.

3. The absence of a public announcement by Cobalt of plans to launch its ANDA product does not establish an intent to forego launch. It merely establishes that Cobalt has not decided to disclose its business plan, which may be a function of uncertainty or a simple desire not to share the plan its competitors.

These simple logical truths reveal the inherent flaw in the proposed intent-to-launch standard. FDA is precluded by elemental due process from confiscating statutory entitlements based on "presumptions" that are little more than guesses. The agency is also precluded, by clear expressions of congressional intent if not by administrative common sense, from demanding firm, enduring, and public commitments that a company

will launch a product and will not consider alternative business options to avoid forfeiture of 180-day exclusivity.

II. Lupin Must Provide a Patent Certification.

Lupin has argued in comments submitted to this docket that it should be permitted to withdraw its paragraph IV certification and to secure effective approval of its ANDA with no certification. The proposal is expressly precluded by the statute and by FDA's regulations.

The statute requires that an 505 (b)(2) NDA and an ANDA contain a certification for each that claims the reference drug (or "listed" drug in the case of an ANDA).[7] The wording of the statute is clear and unambiguous. FDA refers to such patents as "relevant" patents, and its regulations are similarly clear and unambiguous.[8]

The agency's regulations also expressly preclude the withdrawal of a paragraph IV certification until expiration of 180-day exclusivity by providing that "an applicant who has submitted a paragraph IV patent certification may not change it to a paragraph III certification of a patent infringement suit has been filed against another paragraph IV applicant unless the agency has determined that no applicant is entitled to 180-day exclusivity or the patent expires before the lawsuit is resolved or expires after the lawsuit is resolved but before the end of the 180-day exclusivity period."[9]

The agency explained the basis for the regulation as follows:

> [T]he protection 180-day exclusivity should not be undermined by changes from paragraph IV certification or by the filing of original certifications other than paragraph IV certifications. . . . [A] patent is deemed to be relevant under § 314.94(a)(12)(ii) until the end of the term of the patent or applicable 180-day exclusivity period, whichever occurs first. . . . [W]here there is a patent that has been challenged by a paragraph IV applicant, a subsequent applicant *will not be able to file a certification that there is no relevant patent or seek an immediately effective approval until either the patent or the 180-day exclusivity period expires.*[10]

Thus the regulation is intended to ensure that a subsequent paragraph IV applicant will be precluded from withdrawing its paragraph IV certification to avoid exclusivity prior to expiration of the exclusivity period or expiration of the patent. Although the regulation refers specifically to a change from a paragraph IV certification to a paragraph III certification, that is because the statute and regulations make clear that, where a patent

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7 FDCA §§ 505(b)(2)(A), (j)(2)(A)(vii).

8 *See* 21 C.F.R. 314.94(a)(12)(i), (ii).

9 21 C.F.R. 314.94(a)(12)(viii).

10 59 Fed. Reg. 50,338, 50,348 (1994) (emphasis added).

is listed in the Orange Book, the only alternative to a paragraph IV certification is a paragraph III certification.

Lupin argues that it should permitted to file a certification that there are no relevant patents. FDA states in the preamble to the regulation (above) that "a subsequent applicant will not be able to file a certification that there is *no relevant patent* or seek an immediately effective approval . . . ."[11] Lupin argues that it should not be required to submit a paragraph III or paragraph IV certification because the patent owner is precluded from bringing a claim against Lupin. This is simply an assertion that the patent should not be considered relevant with regard to Lupin. Relevance of the patent is not a function of whether a claim can be brought against a particular applicant. It is a function of whether the patent claims the reference drug (or "listed" drug in the case of an ANDA).[12] Furthermore, as noted above, FDA states in the preamble to the regulation that "a patent is deemed to be relevant under § 314.94(a)(12)(ii) until the end of the term of the patent or applicable 180-day exclusivity period, whichever occurs first."[13] Finally, if a determination if invalidity in an infringement suit rendered a patent irrelevant as to the ANDA applicant in the suit, a first filer who obtained such a judgment would have to withdraw its paragraph IV certification and thereby forfeit its exclusivity.

Lupin's request that it be permitted to withdraw its paragraph IV certification is, in effect, a request that it share in Cobalt's 180-day exclusivity. The exclusivity would block the other subsequent ANDA applicants and Lupin and Cobalt would be the only applicants permitted to market during the exclusivity period. In fact, the statute and regulations contemplate the possibility that a subsequent paragraph IV applicant will obtain a judgment that a patent is invalid, and jointly provide a specific incentive for subsequent applicants to pursue such judgments – the triggering of the 180-day exclusivity period. The statutory reward is not shared exclusivity with the first applicant and, as the court held in *Ranbaxy Laboratories LTD v. Leavitt*, "FDA may not . . . change the incentive structure adopted by Congress, for the agency is bound 'not only by the ultimate purposes Congress ha selected, but by the means it has deemed appropriate and prescribed for the pursuit of those purposes.'"[14]

Lupin's attempt to rely on FDA's decision regarding pediatric exclusivity in the case of amlodipine is misguided. In that matter, the agency (and reviewing court) found the statute ambiguous regarding the applicability of pediatric exclusivity to an applicant that successfully defends its infringement suit.[15] Here the wording of the statute is clear with regard Lupin's obligation to submit a certification for the relevant patent. In the amlodipine matter, FDA determined (reasonably in the view of the reviewing court) that the wording of the statutory pediatric exclusivity provision makes clear that an applicant

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11 *Id.* (emphasis added).

12 FDCA §§ 505(b)(2)(A),505(j)(2)(A)(vii).

13 *Id.*

14 469 F.3d 120, 126 (2006).

15 Mylan Laboratories, Inc. v. Leavitt, 484 F. Supp.2d 109, 121 (D.D.C. 2007).

who successfully defends an infringement suit should not be blocked by pediatric exclusivity.[16] Here there is not the slightest suggestion in the statute or legislative history that a subsequent ANDA applicant should evade 180-day exclusivity if that applicant is successful in an infringement suit. Such an interpretation would effectively negate the first applicant's exclusivity, and would be directly contrary to Congress' clearly expressed intent in the 180-day exclusivity provision.

III. There Can Be No Triggering Decision Until After the Mandate Issues.

Lupin argues in its comments that the statutory reference to the "date on which the court of appeals decides that the patent is invalid or not infringed,"[17] which triggers exclusivity, must be interpreted to refer to the date of the appellate court's initial filing of a decision (prior to issuance of the mandate), which is tentative and has no immediate effect, rather than to the date on which the decision becomes final after issuance of the mandate. Lupin argues that this illogical outcome is manifest by Congress' use of the term "decides" rather than he term "determines," which latter term is used in the statutory provision on pediatric exclusivity.[18] This is not the case.

The provision at issue was enacted in the MMA to restore FDA's original interpretation of the court "decision" trigger of the original (1984) 180-day exclusivity provision. In the scenario at issue here, where a district court finds infringement and an appellate court overturns that decision, FDA had interpreted that "decision" to be the decision of a district court that implements the mandate of the appellate court. The agency's 1994 regulation provided as follows:

> For purposes of establishing the effective date of approval based on a court judgment, the following dates shall be deemed to be the date of the final decision of the court on the patent issues . . .
> (iii) If the district court enters a decision that the patent is infringed, and the decision is appealed, the date on which the district court enters a judgment that the patent is invalid, unenforceable, or not infringed pursuant to a mandate issued by a court of appeals. . . .[19]

The agency had to abandon this interpretation, however, in the face of court decisions declaring appellate review irrelevant to determining the triggering court decision.[20] In passing the MMA provision, Congress clearly determined that FDA's original interpretation of the statute set forth in the 1994 regulations expressed Congress' intent regarding the court decision trigger, and restored that interpretation. Congress was obviously aware that, under the agency's interpretation of the court "decision" trigger, the

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16 *Id.*

17 FDCA § 505(j)(5)(B)(iii)(II)(aa)(AA).

18 *See* FDCA § 505A(c)(2)(B).

19 21 C.F.R. 314.107(e) (revoked at 65 Fed. Reg. 43233 ((2000)).

20 *Id.*

triggering "decision" was a final decision that set the rights and obligations of the parties, which in matter at hand would be the district court decision implementing the mandate from the court of appeals.

Respectfully submitted,

David G. Adams
Counsel to Ranbaxy Inc.