

December 23, 2002

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Mark B. McClellan, M.D., Ph.D.  
Commissioner of the Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Re: FDA's Proposed Amendments to 21 C.F.R. Part 314

Dear Dr. McClellan,

Please find attached Kos Pharmaceuticals, Inc.'s comments to the Food and Drug Administration's proposed amendments to 21 C.F.R. Part 314. Kos submits that the FDA's proposed interpretation of §505(j)(2)(B)(iii) of the Hatch-Waxman Act to eliminate the possibility of multiple 30 month stays on ANDA approval should not be maintained. First, the FDA does not need to eliminate the possibility of multiple 30 month stays in order to prevent the improper listing of patents in the Orange Book. Instead, implementation of the proposed amendments that (1) clarify the types of patents that may and may not be listed and (2) require a detailed declaration from the NDA holder will prevent improper listings.

Second, Kos submits that the FDA's proposed new interpretation of subsection (B)(iii) is improper. Subsection (B)(iii) must be read in light of the other sections of the statute, which clearly dictate that an ANDA filer must give the patent holder notice of any Paragraph IV Certification. Also, every added Paragraph IV certification is an amendment regardless of whether the ANDA already contains such a certification. Each Paragraph IV Certification is a unique submission specific to the patent certified to and addresses the ANDA filer's non-infringement, invalidity, and/or unenforceability contentions with respect to that patent.

Third, Kos submits that the elimination of the 30 month stay for legitimately late-listed patents will deprive a patent holder of a statutory remedy for infringement of its patent provided under the Hatch-Waxman Act, will penalize the patentee for delays in patent prosecution that it did not create, and will deprive the courts of their statutory power to determine the necessity of 30 month stays in a given situation. Further, there is little evidence that the elimination of multiple 30 months stays in ANDA litigation will result in greater public availability of generic pharmaceuticals. For the above reasons, Kos submits that the FDA's proposal to eliminate the possibility of multiple 30 months stays for legitimately late-listed patents not be maintained.

Sincerely,

Adrian Adams  
President and CEO  
Kos Pharmaceuticals, Inc.

**Comments Submitted to the  
Food and Drug Administration  
regarding its  
Proposed Amendments to  
21 C.F.R. Part 314**

Submitted by

Kos Pharmaceuticals, Inc.  
1001 Brickell Bay Drive, 25th Floor  
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## I. INTRODUCTION

Kos Pharmaceuticals, Inc. (“Kos”) submits the following comments in response to the Food and Drug Administration’s (“FDA’s”) proposal to amend its patent listing requirements (as enumerated in 21 C.F.R. Part 314) for New Drug Applications (“NDAs”). The FDA has proposed these amendments to deter patents from being improperly listed in the *Approved Drug Products with Equivalence Evaluations* (“the Orange Book”), and, as a result, to prevent delays in the introduction of generic pharmaceuticals onto the market.

The FDA’s proposal would (1) amend FDA regulation 21 C.F.R. § 314.53(b) to limit the types of patents that may be listed in the Orange Book, (2) amend FDA regulation 21 C.F.R. § 314.53(c)(2)(i) to require NDA holders to submit a more detailed declaration when submitting a patent to be listed in the Orange Book, and (3) amend FDA regulations 21 C.F.R. §§ 314.52(a)(3) and 314.95(a)(3) to eliminate the requirement that an Abbreviated New Drug Application (“ANDA”) applicant give notice to a patentee that the ANDA has been amended to include additional Paragraph IV certifications. The FDA has proposed amendment (3) to reflect its new interpretation of § 505(j)(2)(B)(iii) of the Hatch-Waxman Act (codified as 21 U.S.C. § 355(j)(2)(B)(iii)), which it is using to support its position that multiple 30 month stays on the approval of ANDAs should be eliminated.

Kos submits that the FDA’s interpretation of § 505(j)(2)(B)(iii) is incorrect and unnecessary to accomplish the FDA’s goals. Amendment of 21 C.F.R. §§ 314.53(b) and (c)(2)(i) would successfully prevent much of the abuse that the FDA has identified, rendering unnecessary the FDA’s strained interpretation of

§ 505(j)(2)(B)(iii). Furthermore, the FDA over-states the alleged abuse of the patent-listing provisions by ethical companies. Finally, the FDA's proposed interpretation of § 505(j)(2)(B)(iii) would deprive the patentee of fundamental statutory rights and would place an undue burden on the FDA to decide issues that are properly left to the courts.

**II. THE FDA'S PROPOSED AMENDMENTS TO 21 C.F.R. §§ 314.53(b) AND (c)(2)(i) WILL PREVENT THE ABUSES THAT THE FDA HAS IDENTIFIED**

The FDA's proposal to eliminate successive 30 month stays on ANDA approval is unnecessary. The FDA's amendments to 21 C.F.R. §§ 314.53(b) and (c)(2)(i) will effectively prevent the fraudulent Orange Book patent listings perceived by the FDA, thus removing the primary barrier in the marketing of generic pharmaceuticals.

**A. The FDA Can Prevent the Improper Listing of Patents in the Orange Book without Eliminating the Possibility of Successive 30 Month Stays on ANDA Approval**

The FDA has proposed (1) amending 21 C.F.R. §315.53(b) to enumerate the types of patents that may and may not be listed by the NDA holder in the Orange Book, and (2) amending 21 C.F.R. §314.53(c)(2)(i) to require the NDA holder to submit a more detailed declaration than is currently required when submitting a patent for listing in the Orange Book. These two rules, by themselves, will prevent the improper listing of patents in the Orange Book and will ensure that the marketing of generic pharmaceuticals to the public will not be unfairly delayed.

**1. Enumerating the Patents that May and May Not be Listed in the Orange Book by an NDA Holder will Prevent the Improper Listing of Patents in the Orange Book**

Under the new rule proposed by the FDA, the patents that the patentee may list in the Orange Book include: drug substance (ingredient) patents, drug product (formulation and composition) patents, product by process patents, and method of use patents. In addition, in order to be listed, these patents must claim the formulation or method of use of the drug that was described in the drug's NDA. The proposed regulation also identifies the types of patents that the patentee may not list in the Orange Book: process patents or patents claiming packaging, metabolites, or intermediates of the approved drug product.

This amendment would have a significant impact on reducing the number of improper patent listings, and thus accomplish the FDA's objectives. A study by the Federal Trade Commission ("FTC") entitled *Generic Drug Entry Prior to Patent Expiration* ("the Study") found only eight instances where "late-listed patents" have resulted in multiple 30 months stays on ANDA approval.<sup>1</sup> The FDA's proposed amendments would have prevented the patents at issue in four of these eight instances from ever being listed in the Orange Book, thus preventing the issue of multiple 30 month stays from ever arising in such situations.

In three of these situations, the listed patents did not claim the formulation or method of use of the drug that was described in the drug's NDA, and thus could not have been listed under the FDA's proposed amendment. The NDA holder for Tiazac<sup>®</sup>

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<sup>1</sup> A "late-listed patent" is a patent listed in the Orange Book after an ANDA (and any related Paragraph IV certifications) has been filed. The products involved in these late-listed patent situations were Tiazac<sup>®</sup>, Neurontin<sup>®</sup> (tablets and capsules), Buspar<sup>®</sup>, Hytrin<sup>®</sup>, Platinol<sup>®</sup>, Paxil<sup>®</sup>, and Taxol<sup>®</sup>.

late-listed a patent in the Orange Book that allegedly claimed Tiazac's<sup>®</sup> drug substance. However, the formulation disclosed in the patent did not claim the formulation described in the approved NDA for Tiazac<sup>®</sup>.<sup>2</sup> Similarly, the holder of the NDAs for both the tablet and capsule forms of Neurontin<sup>®</sup> late-listed a method patent as covering its drug product, even though this patent did not claim the methods of use for Neurontin<sup>®</sup> that were set forth in its NDAs.

Under the FDA's proposed rules, none of these patents could have been listed in the Orange Book. Both formulation and method of use patents can be listed in the Orange Book only if they claim formulations or methods approved in the NDA of the drug product.

In the fourth situation, the patent at issue could not have been listed under the FDA's proposed amendments because it is one of the types of patents that the FDA would exclude from ever being listed in the Orange Book. In that example, the NDA holder for Buspar<sup>®</sup> late-listed a patent claiming a method of use of a metabolite produced by the administration of Buspar<sup>®</sup>.<sup>3</sup> Under the FDA's proposed rules, patents directed to metabolites may not be listed in the Orange Book, so this patent would not have been listed.

Finally, little empirical evidence exists to suggest that the elimination of multiple 30 month stays in ANDA litigation will result in greater public availability of generic pharmaceuticals. In fact, only 3.8% of all ANDAs (or 17 of the 442 active ANDAs) have been ever been stayed, even once,<sup>4</sup> making the FDA's proposal to

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<sup>2</sup> See *Andrx Pharm., Inc., v. Biovail Corp.*, 276 F.3d 1368, 1373-1376 (Fed. Cir. 2002).

<sup>3</sup> See *Mylan Pharm., Inc., v. Thompson*, 139 F. Supp 2d. 1, 9 (D. Col. 2002).

<sup>4</sup> *A Review of the FTC Report, 'Generic Drug Entry Prior to Patent Expiration': Before the Subcomm. on Health*, Oct. 9, 2002 (statement of the Honorable L. Crawford, Acting Commissioner, U.S. FDA).

eliminate successive 30 month stays at best an ineffective way to address the FDA's concerns. Furthermore, the stay imposed on ANDA approval resulting from patent infringement litigation has not been shown to delay the time that the generic drug is brought to market. The ANDA approval process typically takes about 30 months, regardless of whether or not the ANDA filer has been sued for infringement.<sup>5</sup>

On average, pharmaceutical patents are challenged within five years of their issuance, long before their expiration dates. In many cases, generic drug manufacturers apply for ANDA approval as early as 48 months after NDA approval of the branded drug product.<sup>6</sup> Arguments that branded drug manufactures are abusing the use of multiple 30 month stays to gain extended patent protection for their products are exaggerated and incorrect.

**2. Requiring an NDA Holder to Submit a More Detailed Declaration in Order to List its Patent in the Orange Book Will Prevent the Improper Listing of Patents**

Amending 21 C.F.R. § 314.53(c)(2)(i) to require the NDA applicant to include a more detailed declaration when submitting patent information for listing in the Orange Book will further reduce improper patent listings. Currently, the declaration accompanying a listing provides only that: "The undersigned declares that Patent No. \_\_\_ covers the formulation, composition, and/or method of use of (name of drug product). This product is (currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act) [or] (the subject of this application for which approval is being sought)."

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<sup>5</sup> *A Review of the FTC Report, 'Generic Drug Entry Prior to Patent Expiration': Before the Subcomm. on Health, Oct. 9, 2002* (statement of the Honorable T. Muris, chairman, FTC).

<sup>6</sup> *A Review of the FTC Report, 'Generic Drug Entry Prior to Patent Expiration': Before the Subcomm. on Health, Oct. 9, 2002* (statement of Mr. G. Glover, attorney, Ropes & Gray).

In contrast, the FDA’s proposal for a more detailed declaration would require the patentee to specify whether its patent covers a drug substance, drug product, and/or method of use; to identify the particular patent claims directed to the drug substance, drug product, and/or method of use; and to state that the drug substance, drug product, and/or method of use claimed in the patent is the subject of the NDA. These more detailed requirements will clearly make it more difficult to list a patent improperly.

**III. THE FDA’S INTERPRETATION OF § 505(j)(2)(B)(iii) IS INCORRECT**

The FDA’s proposed new interpretation of § 505(j)(2)(B)(iii) is incorrect. First, § 505(j)(2)(B)(iii) must be interpreted in light of the other sections of the Hatch-Waxman Act.<sup>7</sup> The Act clearly dictates that an ANDA applicant must give the patent holder notice of any Paragraph IV certification, not just the applicant’s original certification. Second, every additional Paragraph IV certification submitted by an ANDA filer after submission of the ANDA should be considered an “amendment” to the ANDA. Each Paragraph IV certification is a unique submission that addresses the ANDA filer’s non-infringement, invalidity, and/or unenforceability contentions with respect to each patent listed in the Orange Book.

**A. The FDA’s Interpretation of § 505(j)(2)(B)(iii) Ignores the Plain Language of the Statute**

Section 505(j)(2)(B)(iii) of the Hatch-Waxman Act provides:

“If an [ANDA] application is amended to include a certification described in subparagraph (A)(vii)(IV), the notice required by clause (ii) shall be given when the amended application is submitted.”

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<sup>7</sup> Title I of the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

Both the courts and the FDA have interpreted § 505(j)(2)(B)(iii) in a uniform manner since its enactment. In general, both have found that, under § 505(j)(2)(B)(iii), an ANDA applicant must submit a certification for each patent listed in the Orange Book. In addition, each time the ANDA applicant submits a Paragraph IV certification, it is required to provide notice of the Paragraph IV certification to the patentee and the NDA holder. Upon receipt of the notice of the ANDA applicant's Paragraph IV certification, the patentee has 45 days to file a patent infringement lawsuit against the ANDA applicant. If the patent holder chooses to file suit, the FDA cannot approve the its ANDA until the earlier of (1) 30 months or (2) a court decision that the patent is invalid or not infringed.<sup>8</sup>

The basis for this interpretation is clear when the provisions of the statute are viewed together. In particular, § 505(j)(2)(A)(vii)(IV) provides that an ANDA filer must submit a Paragraph IV certification for each patent that claims the listed drug that is the subject of the NDA. Sections 505(j)(2)(B)(i) and (iii) require that the ANDA applicant must give notice of each Paragraph IV certification to the NDA holder and the patentee when an amendment is submitted. Moreover, under § 505(b)(3)(A), an ANDA applicant submitting a Paragraph IV certification must include a specific statement in the ANDA application that it will give such notice. This statutory framework is clear. The ANDA applicant is required to give notice of each Paragraph IV certification to the patent holder, regardless of whether the Paragraph IV certification is part of the original ANDA application or an amended ANDA application.

The FDA's proposed interpretation of § 505(j)(2)(B)(iii) requires notice of a Paragraph IV certification to be provided to a patentee only once – either (1) at the time

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<sup>8</sup> 21 U.S.C. §355(c)(3)(C)

the original ANDA is submitted, if it contains a Paragraph IV certification, or (2) the first time an ANDA is amended to include a Paragraph IV certification (but only if the original ANDA does not contain a Paragraph IV certification). The FDA argues that the presence of the term “amended” in the statute means that this section was intended only to apply to an ANDA applicant that did not include a Paragraph IV certification in its original ANDA.

This interpretation is inconsistent with the plain meaning of the statute. Indeed, the FDA admits that its new interpretation is inconsistent with the way it has interpreted § 505(j)(2)(B)(iii) for years. The FDA should continue to interpret § 505(j)(2)(B)(iii) to require notice of a Paragraph IV certification each time such certification is filed.

**B. Every Additional Paragraph IV Certification Submitted by an ANDA Filer after Submission of its ANDA Should be Considered an “Amendment” to the ANDA**

Under 21 C.F.R. § 314.96, an ANDA applicant may amend its unapproved ANDA by (1) revising existing information or (2) providing additional information, including additional Paragraph IV certifications. In the past, each additional Paragraph IV certification has been treated as a separate amendment that has triggered a separate notice requirement. However, the FDA’s new interpretation of the statute treats only the first Paragraph IV certification submitted by an ANDA holder (after the filing of its ANDA) as an amendment.

This view undermines the purpose of a Paragraph IV certification. A Paragraph IV certification is not a broad, generic document to be filed once, as the FDA seems to suggest, but instead a unique document that contains information specific to

each patent that is listed in the Orange Book. Each Paragraph IV certification is directed to one or more specific patents. Each Paragraph IV certification discloses the reasons that the ANDA applicant believes the specific patents addressed are invalid, unenforceable, or will not be infringed by the ANDA product. Thus, a Paragraph IV certification with respect to one patent cannot address later-listed patents. For this reason alone, each Paragraph IV certification should be treated as a separate amendment that gives rise to a separate notice requirement and a separate 30 month stay on ANDA approval.

**IV. THE FDA’S PROPOSED INTERPRETATION OF § 505(j)(2)(B)(iii) WILL UNFAIRLY PENALIZE PATENTEES AND DISCOURAGE INNOVATION**

The elimination of 30 month stays for legitimately late-listed patents will deprive a patent holder of a statutory remedy for infringement of its patents provided under the Hatch-Waxman Act and will penalize the patentee for delays in patent prosecution that it did not create. The FDA’s proposal would also deprive the courts of their statutory power to determine the necessity of 30 month stays in a given situation, thereby discouraging the development of new drugs in general.

**A. The FDA’s Proposed Interpretation Deprives the Patentees of their Statutory Right to Sue for Infringement Resulting from the Filing of an ANDA**

Under 35 U.S.C. § 271(e)(2)(A), it is an act of infringement to submit an ANDA for a drug composition or a method of using a drug that is claimed in a patent. As previously discussed, a patent holder may sue an ANDA applicant for infringement of any patent listed in the Orange Book (even late-listed patents) after receiving notice from the applicant that its ANDA contains a Paragraph IV certification stating that the listed

patents is invalid, unenforceable, and/or not infringed by the ANDA applicant's generic drug product. This statutory provision was part of the balance Congress struck in enacting the Hatch-Waxman Act, which was intended to allow new drugs to be marketed more cheaply and quickly by substantially shortening the time and effort needed to obtain marketing approval of generic drugs.<sup>9</sup>

Under the present regulations, the patentee receives this notice from the ANDA applicant (1) if its ANDA as originally filed contains a Paragraph IV certification, and (2) any time the ANDA applicant supplements or amends its ANDA to contain any additional Paragraph IV certification.

Under the FDA's proposed interpretation, however, the patentee will receive notice that an ANDA applicant has filed a Paragraph IV *only once*. After this initial notice is received, the ANDA filer is under no obligation to give notice to the patent holder that it has amended its ANDA to include additional Paragraph IV certifications, even though the filing of its amended ANDA is a statutory act of infringement. The patentee would thus be deprived of its statutory right to sue for infringement of its legitimately later-listed patent.

This proposed interpretation is in direct conflict with the statutory rights afforded to patentees under § 271(e)(2)(A) and will undermine the carefully considered balance struck by Congress in enacting the Hatch-Waxman Act. In effect, the FDA's proposal to eliminate the notice requirement (in order to eliminate multiple 30 month stays) would undermine established patent law.

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<sup>9</sup> See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990).

**B. The FDA's Amendments Will Unfairly Penalize Patentees for Delays that They Did Not Cause**

Under the amendments, the ANDA applicant does not have to provide notice to the patentee of a Paragraph IV certification of a patent that has been late-listed in the Orange Book when a Paragraph IV certification has previously been filed. However, ultimate control of the timing of patent issuance, and therefore, the date on which a patent will subsequently be listed in the Orange Book, lies with the United States Patent and Trademark Office, not the patentee. Moreover, a patent may be listed in the Orange Book only within a 30 day period following its date of issue. Thus, the patentee's remedies for infringement of its patents are at the mercy of the Patent and Trademark Office and uncertainties regarding the duration of patent prosecution.

In addition, a patent applicant has little incentive to delay the issuance of its patent intentionally. A patent terminates 20 years from its earliest filing date, a policy that encourages the swift prosecution of patents.

**C. The Decision of Whether to Permit Successive 30 Month Stays in ANDA Litigation is Properly Left to the Courts, Not the FDA**

The courts, not the FDA, should determine whether to permit successive 30 month stays in ANDA litigation. The FDA is attempting to assert its regulatory authority in an area traditionally reserved for the judiciary.

Presently, the court in which a suit for infringement of listed patents is pending has the discretion to decide whether a stay in an ANDA case should be extended and whether multiple ANDA cases brought on the same generic drug as a result of later-listed patents should be consolidated for a single trial. Through its proposed interpretation, the FDA is attempting to create a bright line rule that eliminates the

possibility of multiple 30 month stays in all ANDA cases, thus shifting power traditionally reserved for the courts to the FDA.

Courts, however, are in a much better position to determine on a case-by-case basis whether a 30 month stay should be shortened or extended. The court is familiar with the facts of each case, the patents and technology at issue, and the parties' claims and defenses. Indeed, in situations where a second suit is filed on later-listed patents, courts have the power to (and often do) consolidate the suits for a single trial and thus avoid multiple 30 month stays altogether. Consequently, the court, not the FDA, is in the best position to evaluate each of these factors in deciding whether the stay in a particular ANDA case should be extended.

## **V. CONCLUSION**

The FDA should not eliminate the possibility of multiple 30 stays for ANDA approval.

The FDA's strained interpretation of § 505(j)(2)(B)(iii) ignores judicial precedent, its own prior statements, and the basic tenets of statutory construction. Furthermore, its view of the statute undermines the purpose of the Paragraph IV certification that gives rise to a 30 month stay.

The FDA does not need to eliminate the possibility of multiple 30 month stays in order to prevent the improper listing of patents in the Orange Book. Instead, it can rely on its proposed amendments to 21 C.F.R. §§ 314.52(b) and (c)(2)(i) to accomplish that same objective.

The patent system is designed to encourage innovation by rewarding those who disclose their invention to the public with exclusive rights to their invention for a

certain period of time. The FDA's proposal to eliminate multiple 30 month stays will contribute to the overall erosion of intellectual property rights of pharmaceutical companies. If the patent protection afforded to pharmaceutical companies becomes weak, innovation regarding better drug delivery and new methods of use for existing drugs will be chilled. Inventors will have no incentive to further improve or characterize their drugs.

Thus, Kos submits that the FDA's proposed interpretation of § 505(j)(2)(B)(iii) of the Hatch-Waxman Act to eliminate the possibility of multiple 30 month stays on ANDA approval should not be maintained.