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

Re: 180-Day Exclusivity for ANDA 76-052

Supplement to Citizen Petition – Dkt. 2005P-0008

In a pending citizen petition dated January 5, 2005, IVAX Pharmaceuticals, Inc., (IPI) has requested the Food and Drug Administration (FDA) not to approve subsequent ANDAs for simvastatin tablets and to reinstate the Merck & Co., Inc. (Merck) '481 and '520 patents in the Orange Book. These actions will give effect to IPI's right to 180-day exclusivity under the Federal Food, Drug, and Cosmetic Act (FDCA) for four of the five approved strengths of the reference listed drug for simvastatin tablets.

We are aware of a July 31, 2003, letter from Gary Buehler to ANDA applicants for nefazadone hydrochloride tablets explaining FDA's delisting of a patent from Bristol-Myers Squibb's NDA for Serzone. The Serzone letter stated that the delisted patent would not serve as the basis for 180-day exclusivity for any first-filed paragraph IV ANDA for nefazadone tablets. FDA's letter was not discussed in IPI's petition. This supplement provides IPI's views on the letter.

IPI will comment on the Federal Trade Commission's April 5, 2005, response to IPI's petition in a separate submission.

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1. Summary of IPI's simvastatin petition.

IPI submitted the first substantially complete ANDA for simvastatin 5 mg, 10 mg, 20 mg, and 40 mg tablets containing paragraph IV certifications to Merck's '481 and '520 patents. IPI notified Merck and Merck did not sue IPI for patent infringement. Under Mova Pharm. Corp. v. Shalala (Mova), 140 F.3d 1060 (D.C. Cir. 1998), and FDA's regulations as amended in 1998 in response to Mova, IPI's ANDA is eligible for 180-day exclusivity if it was substantially complete when submitted with a paragraph IV certification previous to submission of other paragraph IV ANDAs for simvastatin. IPI believes its ANDA met these conditions as to four of the five dosage strengths of the reference listed drug, and that its right to 180-day exclusivity under § 505(j)(5)(B)(iv) vested when the simvastatin ANDA was received by FDA under 21 C.F.R. § 314.101.

FDA has chosen to give effect to 180-day exclusivity by requiring ANDAs to contain paragraph IV certifications until 180-day exclusivity has expired. For this mechanism to work, patents to which these paragraph IV certifications are made must remain in the Orange Book, even if the NDA holder requests delisting, "until FDA determines that no [180-day] delay . . . is required under the statute." 21 C.F.R. § 314.94(a)(12)(viii)(B). If FDA agrees to delist patents, therefore, it has decided that 180-day exclusivity will not be granted. FDA has delisted the '481 and '520 patents.

FDA apparently delisted the '481 and '520 patents because § 314.94(a)(12)(viii)(B) states that, to be retained in the Orange Book, a patent must be "the subject of a lawsuit under § 314.107(c)." Merck did not sue IPI or other ANDA applicants for infringement of the '481 and '520 patents.

But the lawsuit limitation is anachronistic and cannot lawfully be applied. When § 314.94(a)(12)(viii)(B) was issued in 1994, FDA's regulations conditioned eligibility for 180-day exclusivity on the paragraph IV ANDA applicant's having successfully defended against an NDA holder's lawsuit for infringement of the patent to which the paragraph IV certification related. That condition was stated in § 314.107(c). The reference in

§ 314.94(a)(12)(viii)(B) to a patent that "is the subject of a lawsuit" is to the patent in the "suit for patent infringement" against which the ANDA applicant had to successfully defend to meet the condition in § 314.107(c).

After the successful defense condition of § 314.107(c) was struck down in Mova in 1998, FDA amended § 314.107(c) to omit the successful defense, or any lawsuit, condition, but it did not amend § 314.94(a)(12)(viii)(B). Nevertheless, FDA cannot continue to apply § 314.94(a)(12)(viii)(B) as if Mova were never decided. The lawsuit condition in § 314.94(a)(12)(viii)(B) is a cross-reference to the lawsuit condition in § 314.107(c) and serves no purpose other than to give effect to180-day exclusivity in accordance with § 314.107(c). Applying the literal text of § 314.94(a)(12)(viii)(B) has the effect of reviving FDA's pre-Mova version of § 314.107(c) each time an NDA holder requests delisting of an unlitigated paragraph IV patent.

The NDA holder's interest in correct patent listings has no relevance to whether a patent must remain in the Orange Book after it has been the subject of a paragraph IV certification. The patent must remain there, not because it is relevant under sections 505(b)(1) and (c)(2), but because FDA's mechanism for enforcing an ANDA applicant's 180-day exclusivity under section 505(j)(5)(B)(iv) requires that it remain listed. After Mova, this reason applies just as much to unlitigated patents as it does to those that are the "subject of a lawsuit."

In any event, even if FDA believes that the physical delisting of patents that support 180-day exclusivity should be permitted, it must, under Mova, still give effect to the 180-day exclusivity of an eligible ANDA applicant by considering the delisted patents as – in the FDA's own words in the 1994 preamble to § 314.94(a)(12)(viii)(B) – "deemed to be relevant" for purposes of enforcing this statutory right. FDA used the quoted phrase in recognition that patents would continue to be listed not because they qualified under sections 505(b)(1) and (c)(2) – a judgment left to NDA holder – but because they are the technical predicate to ANDA applicants' eligibility for 180-day

exclusivity – a matter not subject to the judgment of NDA holders, but determined instead by § 314.107(c) as revised after Mova.

2. The Serzone letter.

Bristol-Myers Squibb (Bristol) is the holder of an NDA for nefazadone hydrochloride tablets, marketed as Serzone. Bristol listed the '664 patent. Several ANDA applicants made paragraph IV certifications to the '664 patent, notified Bristol, and were not sued for infringement. Bristol then requested removal of the '664 patent from the Orange Book. FDA agreed to the request. By letter dated July 31, 2003, to ANDA applicants for nefazadone tablets, FDA explained its decision.

The FDA letter said that Bristol's request to delist the '664 patent was not prohibited by § 314.94(a)(12)(viii), because the patent was not the subject of a lawsuit under section 505(j)(5)(B)(iv). The letter said that although FDA amended § 314.107(c) after Mova, the agency "retained the requirement of a lawsuit having been filed in this context," referring to the context of a patent delisting at the NDA holder's request.

The FDA letter said that the language the Mova court found compelling "is not directly applicable to this circumstance." "Instead," the letter continued, "the only applicable statutory provision generally gives control over patent listings to the NDA holder," referring to section 505(b)(1) and (c)(2). The letter characterized its interpretation – not allowing patent delisting when there is an infringement lawsuit, but allowing patent delisting when there is no lawsuit – as a "reasonable balance between allowing NDA applicants to correct patent listings and protecting the incentive for ANDA applicants who are sued as a result of a patent certification and bear the cost of that litigation."

With respect to 180-day exclusivity, the FDA letter said that the agency had no obligation to maintain a patent listing solely because an ANDA applicant could, under Mova, establish eligibility "merely by submitting a paragraph IV patent challenge." The

FDA letter said that, even if the agency believed that leaving unlitigated patents in the Orange Book despite the NDA holder's delisting request would be "reasonable," FDA would not do so given the language of sections 505(b)(1) and (c)(2). The letter concluded that "[t]he '664 patent will not serve as the basis for 180-day exclusivity."

3. Comment on the Serzone letter.

The Serzone letter is based on the assumption that a paragraph IV ANDA remains eligible for 180-day exclusivity because a patent is kept in the Orange Book. In fact, it is the other way around. Patents are kept in the Orange Book under § 314.94(a)(12)(viii)(B) because – and only because – they are "deemed to be relevant" for the purpose of giving effect to an eligible ANDA applicant's right to 180-day exclusivity." FDA clearly stated this in the preamble to the final Hatch-Waxman regulations, 59 Fed. Reg. 50,338, 50,348 (Oct. 3, 1994) (quoted in the IPI petition at pp. 4-5), and in its 2003 letter to Apotex and Purepac on 180-day exclusivity for gabapentin ANDAs (described in the IPI petition at p. 14).

The paragraph IV ANDAs for nefazadone were eligible for 180-day exclusivity, and therefore the '664 patent should have been kept in the Orange Book. FDA's decision to the contrary, as explained in the Serzone letter, was based on a mistaken interpretation of the purpose of § 314.94(a)(12)(viii)(B) in relation to § 314.107(c), and on considerations the Mova court determined were incompatible with the eligibility conditions for 180-day exclusivity under the FDCA.

First, the Serzone letter states that in 1998, in response to Mova, FDA amended "some" of its regulations to remove the successful defense requirement but "retained the requirement of a lawsuit having been filed in this context," i.e., the context of § 314.94(a)(12)(viii)(B). The quoted statement implies that FDA made an affirmative, policy-based decision to "retain" the lawsuit requirement in § 314.94(a)(12)(viii)(B), and that the "context" of § 314.107(c) is different from the "context" of § 314.94(a)(12)(viii)(B). But there is no evidence that FDA thought about the effect of

Mova on the "subject of a lawsuit" phrase in § 314.94(a)(12)(viii)(B). Given that § 314.94(a)(12)(viii)(B) explicitly cross-references § 314.107(c), and § 314.107(c) contained the successful defense condition struck down in Mova, it would be expected that if FDA had believed the lawsuit condition should be retained in the "context" of delisting patents, there would be an explanation of the basis for that belief in FDA documents issued to comply with Mova. No explanation appears in FDA's June 1998 guidance or November 1998 interim rule, however, where § 314.94(a)(12)(viii)(B) is not even mentioned. The only plausible conclusion, therefore, is that FDA did not "retain" the lawsuit requirement for continued patent listing, but simply neglected to remove it.

If the Serzone letter is correct that FDA affirmatively decided to retain the lawsuit requirement in § 314.94(a)(12)(viii)(B), the agency did so either on a misinterpretation of Mova or in disregard of its underlying logic. For, contrary to the Serzone letter's suggestion that patent delisting is one context whereas 180-day exclusivity is another, both § 314.94(a)(12)(viii)(B) and § 314.107(c) are part of the same context – the context of what conditions apply to eligibility for 180-day exclusivity. Section 314.107(c) establishes the eligibility conditions for exclusivity. Section 314.94(a)(12)(viii)(B) assures that the exclusivity for which eligibility is established under § 314.107(c) is given effect despite an NDA holder's delisting request. Because §§ 314.107(c) and 314.94(a)(12)(viii)(B) are not different contexts but two parts of one context, the same conditions must apply in both regulations. Therefore, the lawsuit condition removed from § 314.107(c) after Mova cannot continue to govern patent delisting under § 314.94(a)(12)(viii)(B).

Second, if the Serzone letter were correct that 180-day exclusivity is the result of keeping patents in the Orange Book rather than the reason for requiring them to remain listed, there would necessarily be other factors, besides supporting eligibility for 180-day exclusivity, that the drafters of the regulations must have considered relevant when they wrote § 314.94(a)(12)(viii)(B) to prohibit the delisting of litigated patents. But the only factor the Serzone letter identifies is "allowing NDA applicants to correct patent listings."

Giving NDA holders the option of correcting patent information cannot be the reason for the rule against patent delisting in § 314.94(a)(12)(viii)(B), because that is the one purpose FDA explicitly ruled out in the preamble to the 1994 final regulations: "To ensure that this [evasion of a first applicant's 180-day exclusivity] does not occur, the agency has required that a patent remain on the list after being declared invalid or unenforceable until the end of the 180-day exclusivity period. This means 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." 59 Fed. Reg. at 50,348. In other words, the patents FDA will not delist are the very ones whose listings are incorrect.

Assuring the accuracy of patent listings, therefore, cannot be a factor relevant to § 314.94(a)(12)(viii)(B), and the Serzone letter identifies no other factor as a reason why § 314.94(a)(12)(viii)(B) would be regarded as a different "context" from 180-day exclusivity so as to explain a decision by FDA to "retain" the lawsuit requirement there despite deleting it from § 314.107(c).

Third, if keeping patents listed in the Orange Book is based on factors other than the need to support 180-day exclusivity, there must be a distinction between litigated and unlitigated patents that relates to those factors. However, other than saying that litigating a patent makes a first applicant more worthy of 180-day exclusivity (see below), the Serzone letter does not explain why litigated patents should remain in the Orange Book despite the NDA holder's request to remove them whereas unlitigated patents should be delisted. With respect to the only factor mentioned in the Serzone letter, the accuracy of patent listings, any difference between litigated and unlitigated patents works against FDA's position: the listings of litigated patents that are required to remain in the Orange Book to support 180-day exclusivity are likely to be incorrect, as the mirtazipine and brimonidine examples illustrate (see IPI petition at pp. 10-11). Yet, according to the Serzone letter, the litigated patents are the ones whose listings NDA holders are specifically not allowed to correct. This paradox underlines the fact that, contrary to the

Serzone letter, the prohibition in § 314.94(a)(12)(viii)(B) against delisting patents has no independent purpose unrelated to maintaining an ANDA applicant's eligibility for 180-day exclusivity. This fact is explicit in the 1994 preamble explanation and in the cross-reference to § 314.107(c) in the codified text. Because the sole purpose of requiring patents to remain in the Orange Book despite an NDA holder's delisting request is to support eligibility for 180-day exclusivity under § 314.107(c), Mova requires that unlitigated patents remain listed as well as litigated patents.

Fourth, the Serzone letter says that Mova is not relevant to whether a patent can be delisted at the NDA holder's request, because Mova was based on an interpretation of section 505(j)(5)(B)(iv) whereas NDA holders request listing and delisting under sections 505(b)(1) and (c)(2). But the issue in Mova did not involve patent listing under sections 505(b)(1) and (c)(2). It involved eligibility for 180-day exclusivity. The Mova court held that FDA could not limit eligibility by requiring a successful defense against a lawsuit. In reaching that conclusion, the court had no need to address the mechanism FDA uses to give effect to an ANDA's eligibility for exclusivity once that eligibility has been established in accordance with the court's holding and FDA's regulations. That mechanism consists of keeping patents listed in the Orange Book despite an NDA holder's delisting request.

Although the Serzone letter states that the "statutory language [gives] control over patent listings to the NDA holder," sections 505(b)(1) and (c)(2) have nothing to do with continued patent listing as part of FDA's mechanism for giving effect to an ANDA applicant's statutory right to exclusivity. Even if the Serzone letter were correct on this point, sections 505(b)(1) and (c)(2) are equally relevant to litigated patents and unlitigated patents, and the NDA holders should be as entitled under § 314.53 to delist paragraph IV patents that are the "subject of a lawsuit" as FDA believes they are to delist unlitigated paragraph IV patents. There is no "subject of a lawsuit" exception in sections 505(b)(1) and (c)(2), or in § 314.53. In fact, the prohibition against patent delisting was included in the regulations to implement section 505(j)(5)(B)(iv), and only for that

reason. After Mova, the prohibition must apply to paragraph IV patents whether they are the subject of a lawsuit or not.

Fifth, other than the accuracy of patent listings – a factor that applies equally to litigated and unlitigated patents – the only reason given in the Serzone letter for distinguishing between litigated and unlitigated patents with respect to delisting is the superior entitlement to 180-day exclusivity of paragraph IV ANDA applicants that are sued for patent infringement. The letter defends delisting Bristol's '664 patent as part of a reasonable balance that, on the generic drug side, includes "protecting the incentive for ANDA applicants who are sued as a result of a patent certification and bear the cost of that litigation." The letter notes that it should not be obliged to maintain patent listings to support 180-day exclusivity because an ANDA applicant "may be eligible . . . merely by submitting a paragraph IV patent challenge," but no litigation results.

The Serzone letter's creation of two classes of first-filed paragraph IV ANDAs based on whether an ANDA applicant is sued for infringement is at odds with Mova. Before Mova, FDA awarded 180-day exclusivity only to applicants that successfully defended against lawsuits. FDA argued in Mova that this condition was justified by, among other factors, the fact that applicants who were sued and won deserved the reward whereas those who were not sued did nothing to earn it. The Mova court rejected FDA's arguments, and held that first-filed paragraph IV ANDAs entitled their sponsors to 180-day exclusivity whether or not they successfully defended against patent infringement lawsuits. FDA revised § 314.107(c) to require only that the ANDA contain a paragraph IV certification to qualify under the exclusivity provision of the statute.

Given these decisions, all ANDA first filers stand on equal footing in their eligibility for 180-day exclusivity. Therefore, FDA cannot administer the exclusivity provisions to give superior rights to first filers that have been sued without directly contravening the holding of the Mova court and § 314.107(c) as amended in response to Mova.

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For the reasons above and in IPI's January 5, 2005, citizen petition, the actions requested in the citizen petition should be taken.

Respectfully submitted,

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