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October 3, 2007

BY FEDERAL EXPRESS

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

Re: Docket No. 2007N-0311 – Midodrine Hydrochloride Exclusivity Issues

Dear Sir or Madam:

Apotex Inc. hereby submits these comments in response to the Food and Drug Administration's (FDA's) solicitation of views concerning the availability of 3-year exclusivity for companies with approved Abbreviated New Drug Applications (ANDAs) for Midodrine Hydrochloride Tablets that conduct a Phase 4 study to verify the clinical benefit of the Midodrine Hydrochloride Tablets. The response was requested by the FDA in lieu of the ANDA#77-746 for Midodrine Hydrochloride Tablets.¹ The response by Apotex Inc. is similar to and reflects the thinking of the other generic manufacturers who are a part of the consortium of companies that have decided to conduct a Phase 4 study to verify the clinical benefit of the Midodrine Hydrochloride Tablets.

The FDA approved Shire's PROAMATINE Tablets, the Reference Listed Drug ("RLD") for ANDA #76-725, on September 6, 1996 (NDA #19-815) under the Agency's "accelerated approval" regulations at 21 C.F.R. part 314, subpart H (surrogate endpoint) for the treatment of symptomatic Orthostatic Hypotension (OH). To date, Shire has not obtained FDA approval for the required Phase 4 studies necessary to verify clinical benefit. The FDA has indicated that "[i]f those studies are not approved in a timely manner, that NDA (and all ANDAs referencing that NDA) will be subject to withdrawal under the withdrawal provisions of subpart H (§ 314.530)." FDA Letter, Docket #2007N-0311. As a result, Apotex Inc. and other ANDA holders are considering whether to collaborate to complete the required Phase 4 studies to verify clinical benefit for Midodrine Hydrochloride. At FDA's request, Apotex Inc. and other Midodrine Hydrochloride stakeholders met with Agency officials in March 2007 to discuss the studies needed to determine the clinical effectiveness of Midodrine Hydrochloride. At that meeting, FDA "made it clear that the Agency regarded both Studies 401 and 404 as 'failed' studies and was not likely to change this interpretation, but the Agency certainly thought there was a good possibility that further studies could show an effect of Midodrine."² At the meeting,

¹ In responding to FDA's questions, Apotex assumes that Shire Laboratories Inc. ("Shire") will not conduct the requisite Phase 4 studies. See FDA, March 8, 2007 Joint Meeting Minutes, at 4 (Apr. 19, 2007) ("In response to a question regarding their plans for the ProAmatine NDA, Shire stated that they were considering withdrawal of the drug from the market, and this was likely. Shire stated that the most likely scenario was that they would not conduct further clinical studies.").

² Shire conducted two Phase 4 studies and submitted the results to FDA in 2005: (1) Study SPD426-401 (A Multi-Center, Double-Blind, Randomized, Placebo-Controlled

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FDA also raised the possibility of 3-year exclusivity for ANDA holders who complete the required Phase 4 studies, but noted that the issue had not yet been fully discussed among Agency officials.

As explained below, in Apotex Inc. response to each of the six sets of FDA's questions, the Agency should grant 3-year exclusivity as an incentive to the ANDA sponsors who collaborate to complete the required Phase 4 Midodrine Hydrochloride studies, and provided such studies verify clinical benefit and meet the statutory and regulatory 3-year exclusivity requirements. Apotex Inc. participation and the initiation of the phase 4 Midodrine Hydrochloride studies would be dependent on FDA's decision on granting exclusivity to the participating companies.

- 1. If the post-marketing studies have been previously required as a condition of continued approval of Midodrine Hydrochloride under subpart H and one or more ANDA applicants complete those studies, are those studies eligible for 3-year exclusivity? Under what theory?**

If one or more ANDA applicant conducts the requisite Phase 4 studies, and provided such studies verify clinical benefit of Midodrine Hydrochloride and meet the 3-year exclusivity criteria, then FDA should grant 3-year exclusivity. The market exclusivity is the incentive that would be a motivation for the Apotex Inc. and other Generic companies to conduct the clinical studies.

Under the Federal Food, Drug, and Cosmetic Act (FDC Act) and FDA's implementing regulations, a sponsor may qualify for a 3-year period of marketing exclusivity for an application (either a "full" 505(b)(1) NDA, a 505(b)(2) application, or a supplemental NDA) if the application is for an active moiety that FDA has previously approved and if the application contains "reports of new clinical investigations (other than bioavailability studies)," that were "essential to approval" of the application, and that were "conducted or sponsored by" the applicant. FDC Act §§ 505(c)(3)(E)(iii), (iv), 505(j)(5)(F)(iii), (iv); see also 21 C.F.R. §§ 314.108(b)(4), (5). All three of these criteria must be satisfied in order to qualify for 3-year exclusivity. See 21 C.F.R. § 314.50(j)(4). Each criterion is defined in FDA's implementing regulations.³

Crossover Study to Assess the Clinical Benefit of Midodrine Hydrochloride in Patients with Neurogenic OH); and (2) Study SPD426-404 (A Multi-Center, Double-Blind, Randomized, Placebo-Controlled Crossover Study to Assess the Clinical Benefit of Midodrine HCl in Patients with Moderate to Severe Neurogenic OH).

³ A "new clinical investigation" is:

an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

Id. at § 314.108(a).

An investigation is "essential to approval" of an application if "there are no other data available that could support approval of the application." Id. Finally, an investigation is "conducted or sponsored by the applicant" if "before or during the investigation, the



The FDA has long interpreted the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) ("Hatch-Waxman Act"), which amended the FDC Act, to permit generic applicants to submit supplemental NDAs to their ANDAs that are eligible for 3-year exclusivity.⁴ For example, the FDA stated in a 1987 letter concerning "the statutory mechanism by which ANDA applicants may make modifications in approved drugs if the modifications require the submission of clinical data" that:

If the applicant has an approved ANDA for the approved indications, agency policy permits the applicant to submit a supplemental application that contains reports of clinical investigations needed to support approval of the new indication. Because such a supplement would require the review of clinical data, FDA would process it as a submission under [FDC Act] section 505(b)(2). Because these submissions will be reviewed as applications under section 505(b), they will be subject to the statutory and regulatory requirements applicable to such applications, including the patent filing requirements of sections 505(b) and (c). These submissions also may be eligible for three years of exclusivity provided such studies verify clinical benefit of the drug.

Letter from Paul D. Parkman, M.D., Acting Director, Center for Drugs and Biologics, FDA, to All NDA and ANDA Holders and Applicants, at 1-2 (Apr. 10, 1987).

Although rare, we are aware of a handful of cases in which ANDA applicants have submitted supplements under FDC Act § 505(b) and FDA has granted 3-year exclusivity:

- In March 1998, FDA approved § 505(b) supplements to ANDA #s 83-209 and 86-715 for ESTRATAB (estrogens, esterified) Tablets and granted Solvay Pharmaceuticals, Inc. periods of 3-year exclusivity for the treatment of osteoporosis.

applicant was named . . . as the sponsor of the [IND] . . . under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation." Id.

These definitions are intended to limit the availability of three-year exclusivity to applications supported by "investigations that require a considerable investment of time and money . . . and that are necessary for approval of important innovations requiring substantial study." FDA, Proposed Rule, Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,899 (July 10, 1989) (hereinafter "Proposed ANDA Regulations"). With respect to the kinds of investigations that may qualify for 3-year exclusivity, FDA has stated that they need not be adequate and well-controlled studies and that such investigations include clinical studies that establish that a product is safer than originally thought and that permit broader use of a drug product. See FDA, Citizen Petition Response, Docket No. #1995P-0366, at 3-4 (Oct. 31, 1996); Proposed ANDA Regulations at 28,899.

⁴ Indeed, FDA's question #4 presumes this: "If 3-year exclusivity is available for the required phase 4 studies and holders of approved ANDAs collaborate to conduct those studies . . . can the first applicant to obtain approval of its supplement selectively waive its 3-year exclusivity in favor of the other collaborators on the studies?" Docket No. 2007N-0311, at 1 (emphasis added).



- In June 1997, FDA granted Ascent Pediatrics, Inc. 3-year exclusivity for a § 505(b) supplemental application for PRIMSOLOL (trimethoprim HCl) Oral Solution (ANDA #74-374) for the treatment of acute otitis media in pediatric patients.
- In November 1992, FDA granted Pharmacia & Upjohn 3-year exclusivity for § 505(b) supplemental applications for OGEN (estropipate) Tablets (ANDA #83-220) for the prevention of osteoporosis.
- In September 1992, FDA approved § 505(b) supplements to ANDA #s 84-499 and 84-500 for ESTRACE (estradiol) Tablets and granted Bristol Myers Squibb periods of 3-year exclusivity for the prevention of osteoporosis.

In this case is that the studies are conducted, verify clinical benefit of Midodrine Hydrochloride and meet the statutory and regulatory criteria for granting 3-year exclusivity. The Midodrine Hydrochloride Phase 4 studies are clearly "essential to approval," and provided such studies are "new clinical investigations" (which is also clearly the case here) and are "conducted or sponsored by the applicant" (discussed below in response to question set #5), there is no legal basis for the FDA to deny 3-year exclusivity.

2. Does the answer to #1 depend on whether the studies merely validate the use of the surrogate endpoint or change the indication or other condition of use for the approved drug product?

The FDA should grant 3-year exclusivity regardless of whether the Midodrine Hydrochloride Phase 4 studies "verify and describe [the drug's] clinical benefit," 21 C.F.R. § 314.510,⁵ or change the indication or other condition of use for the approved drug product, provided such studies meet the statutory and regulatory criteria for granting such exclusivity. A "significant innovation" or a "new condition of use" is not required for a sponsor to be eligible for 3-year exclusivity.

There are several cases in which FDA granted 3-year exclusivity for Phase 4 "accelerated approval" studies conducted by the NDA sponsor.⁶ Although in each instance the requisite

⁵ See FDA, Final Rule, New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942, 58,945 (Dec. 11, 1992) ("[I]t will be the sponsor's clear obligation to resolve any doubts as to the clinical value by carrying out definitive studies."), 58,948 ("The regulations are clear in requiring that, for drugs approved under these provisions based on surrogate endpoints, the post marketing studies must show clinical benefit, not just the previously shown effect on the surrogate.") (citations omitted).

⁶ Such cases include the following:

- NDA #21-602; VELCADE (bortezomib) Injection: NDA Supplement 006, approved on March 25, 2005, fulfilled the sponsor's Subpart H commitments and provided for the use of VELCADE for the treatment of multiple myeloma patients who have received as least one prior therapy. FDA granted 3-year exclusivity for the "expanded indication to include treatment of multiple myeloma patients who have received at least 1 prior therapy."



Phase 4 studies supported approval of a new or modified indication, the types of changes eligible for 3-year exclusivity are not limited to significant changes for the approved drug product (e.g., a new indication or other new condition of use), but also include a change in the status of a drug product (e.g., an Rx-to-OTC switch, or a change from Subpart H approval status to non-Subpart H approval status). Indeed, FDA has stated that an argument that:

a "significant innovation" or a "new condition of use" is required to receive marketing exclusivity for a change under [FDC Act §§ 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv)] is incorrect. Under these paragraphs of [FDC Act § 505], a "change" approved in a supplement to a 505(b) application is awarded marketing exclusivity for three years if the supplement is approved after September 24, 1984; the supplement contains "reports of new clinical investigations (other than bioavailability studies)"; the investigations are "essential to the approval of the supplement"; and the investigations are "conducted or sponsored by the person submitting the supplement." Thus, the standard under the [FDC Act] for determining whether a change in a supplement is granted marketing exclusivity is whether the change is supported by new clinical investigations that are essential to the approval of the supplement.

FDA, Citizen Petition Response, Docket No. #1995P-0366, at 2 (Oct. 31, 1996) (emphasis added), 3 ("This interpretation of the statute is fully consistent with the intent of Congress."). Although this FDA decision was not made in the context of a drug product approved under the Agency's "accelerated approval" regulations (but rather in the context of an Rx-to-OTC switch), such a distinction is irrelevant for purposes of 3-year exclusivity eligibility. FDA must apply the same legal criteria for exclusivity in an "accelerated approval" case as in the case of a "traditional" approval.

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- NDA #21-492; ELOXATIN (oxaliplatin) Injection: NDA Supplement 002, approved on January 9, 2004, fulfilled one of the sponsor's Subpart H commitments and provided for the use of ELOXATIN in combination with infusional 5-FU/LV for the treatment of patients previously untreated for advanced colorectal cancer. FDA granted 3-year exclusivity for "ELOXATIN in combination with infusional [5-FU/LV] for the treatment of patients previously untreated for advanced colorectal cancer."
 - NDA #21-029; TEMODAR (temozolomide) Capsules: NDA Supplement 008, approved on March 15, 2005, fulfilled the sponsor's Subpart H commitments and provided clinical support for the use of TEMODAR for the treatment of patients with newly diagnosed high grade gliomas concomitantly with radiotherapy and then as adjuvant treatment. FDA granted 3-year exclusivity for the "treatment of patients with newly diagnosed high grade gliomas concomitantly with radiotherapy and then as adjuvant treatment."
 - NDA #20-896; XELODA (capecitabine) Tablets: NDA Supplement 010, approved on September 7, 2001, fulfilled the sponsor's Subpart H commitments and provided for the use of XELODA in combination with TAXOTERE (docetaxel) for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy. FDA granted 3-year exclusivity for "breast cancer combination therapy."



If one or more ANDA holder conducts the requisite Phase 4 studies to verify the clinical benefit of Midodrine Hydrochloride, and provided such studies verify clinical benefit and meet the 3-year exclusivity criteria, then FDA should grant 3-year exclusivity. Such exclusivity would apply with respect to whatever change might be approved, regardless of whether such a change is a "new condition of use" or verifies and describes clinical benefit.⁷

3. Does the same result apply if the sponsor of the NDA, itself, completes phase 4 studies that were required as a condition of approval under subpart H? Why or why not?

Apotex Inc. and the ANDA holders' decision to conduct the phase IV studies were based on the decision by Shire not to conduct the studies to verify clinical benefit of Midodrine Hydrochloride. Therefore, we believe it is not required for us to address this issue.

4. If 3-year exclusivity is available for the required phase 4 studies and holders of approved ANDAs collaborate to conduct those studies, is there legal authority to permit them to share 3-year exclusivity? If not, can the first applicant to obtain approval of its supplement selectively waive its 3-year exclusivity in favor of the other collaborators on the studies?

Although we are not aware of any legal authority that would permit midodrine HCl ANDA holders that collaborate to conduct the required Phase 4 studies to share the same 3-year exclusivity period based on such studies,⁸ there is legal authority permitting the first ANDA applicant to

⁷ The "change" that might result in FDA granting 3-year exclusivity for the required Phase 4 midodrine HCl studies is not the same type of change involved in a so-called "DESI-upgrade." Under FDA's Drug Efficacy Study Implementation ("DESI") review, a "DESI upgrade" reaffirms FDA's approval of a pre-1962 NDA if the sponsor submits an NDA supplement confirming the drug product's indications for use to those determined to be effective under the DESI review. "[FDA] believes as a matter of policy and statutory interpretation that a grant of exclusivity is inappropriate for any DESI upgrade. . . . A DESI upgrade does not constitute a change in a marketed drug or a major innovation; rather it permits the continued marketing of an already existing product for an already existing indication." Proposed ANDA Regulations at 28,901; see also FDA Citizen Petition Response, Docket No. 1987P-0118, at 8 (Aug. 9, 1988) ("Congress carefully limited the 3-year exclusivity provisions pertaining to NDA supplements to those changes for which new clinical investigations are essential. A DESI upgrade merely permits the continued marketing of a product for an already existing indication. The supplement that allows approval of a DESI NDA or ANDA for effectiveness does not require a change as required by [the FDC Act].") (emphasis in original). In contrast, the type of "change" involved in verifying and describing the clinical benefit of a Subpart H drug (as opposed to merely reaffirming approval) would qualify for 3-year exclusivity, because the requisite Phase 4 clinical studies are essential to approval of the application.

⁸ Indeed FDA has rejected the possibility of multiple claims of exclusivity based on the same study. See FDA, Final Rule, ANDA Regulations; Patent and Exclusivity



obtain approval of its supplement to selectively waive its 3-year exclusivity in favor of the other application sponsors (and specifically in this case, other Phase 4 study collaborators).

The FDA has a long-standing and consistent practice of permitting sponsors to selectively waive 3-year exclusivity. For example, FDA commented in the Agency's Final ANDA Regulations that:

New drug exclusivity is not a property right, but is rather a statutory obligation on the agency. This statutory obligation is based on data and information in an approved application. Although an applicant may purchase an application or rights to data and information in an application (i.e., exclusive rights to a new clinical investigation), from which exclusivity would flow, there is no property right to exclusivity itself that can be transferred separately and apart from the application or data upon which exclusivity is based. The agency does, however, permit the submission or approval of an ANDA when the holder of the exclusivity permits FDA to receive or approve the ANDA.

The FDA affirmed this policy as recently as 2004. Specifically, in a citizen petition response supporting the waiver and relinquishment of 180-day generic drug exclusivity, the FDA cited several examples of cases dating back to 1988 in which the Agency allowed companies to waive (selectively) 3-year exclusivity, 5-year new chemical entity exclusivity, and pediatric exclusivity. See FDA Citizen Petition Response, Docket No. 2004P-0227, at 9-11 (July 2, 2004). There are no unique facts in the case of Midodrine Hydrochloride that would suggest or require a different statutory interpretation. Therefore, if the FDA grants 3-year exclusivity to the first ANDA sponsor that obtains approval of a § 505(b) supplement, that sponsor may selectively waive its exclusivity in favor of the other study collaborators.

5. Under the statute and applicable regulations, could a study be “conducted or sponsored by the applicant” as required for 3-year exclusivity if that applicant paid less than 50 percent of the costs of the study? Why or why not?

The FDA's NDA and supplement content and format regulations at 21 C.F.R. § 314.50(j) (“claimed exclusivity”) and new drug product exclusivity regulations at 21 C.F.R. § 314.108(b) define the eligibility criteria for 3-year exclusivity provided by operation of FDC Act §§ 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv). In particular, these regulations state that an investigation is “conducted or sponsored by the applicant” if:

before or during the investigation, the applicant was named in Form FDA 1571 filed with FDA as the sponsor of the [IND] under which the investigation was conducted,

Provisions, 59 Fed. Reg. 50,338, 50,358 (Oct. 3, 1994) (hereinafter “Final ANDA Regulations”) (“FDA emphasizes that the applicant must have exclusive rights to the purchased study in order to be deemed to have sponsored a study. The purchase of nonexclusive rights by different parties could result in multiple claims of exclusivity for the same study.”) (“A study can be conducted by or for only one applicant. Exclusivity based on less than 50-percent funding would allow multiple parties to claim exclusivity against ANDA applicants as well as each other.”).



or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation. To demonstrate "substantial support," an applicant

must either provide a certified statement from a certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. . . .

21 C.F.R. § 314.108(a) (emphasis added); accord 21 C.F.R. § 314.50(j)(4)(iii).⁹

The FDA commented on the second basis of this regulation (underlined text above) in the preamble to the Agency's Proposed and Final ANDA Regulations. Specifically, the FDA stated that "[i]n rare cases, the applicant may have provided less than 50 percent and still show 'substantial support,' if, for example, the study was extraordinarily expensive and the applicant's contribution to the total cost was significant."

The FDA's comments (as well as the text of 21 C.F.R. §§ 314.50(j)(4)(iii) and 314.108(a)) indicate that such an evaluation is made on a case-by-case basis.

We are not aware of an instance in which FDA granted 3-year exclusivity to an applicant where the "new clinical investigation" that was "essential to approval" was jointly financed by several sponsors and no single sponsor provided 50% or more of the cost of conducting the study; however, certainly the case with Midodrine Hydrochloride is one of the rare instances in which FDA should consider the financial contribution of one ANDA applicant to provide the "substantial support" necessary to show that the requisite Phase 4 study was "conducted or sponsored by the applicant." As a Subpart H drug, Midodrine Hydrochloride is intended for a serious and life-threatening disease that FDA determined provides a meaningful therapeutic benefit to patients over existing treatments. See 21 C.F.R. § 314.500. Because Apotex and the other ANDA

⁹ 21 C.F.R. § 314.50(j)(4)(iii) states:

If the applicant was the sponsor named in the Form FDA-1571 for an [IND] under which the new clinical investigation(s) that is essential to the approval of its application was conducted, identification of the IND by number. If the applicant was not the sponsor of the IND under which the clinical investigation(s) was conducted, a certification that the applicant or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its application, and information supporting the certification. To demonstrate "substantial support," an applicant must either provide a certified statement from a certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation of why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug.



holders assumes that Shire will not conduct the required Phase 4 studies to verify and describe Midodrine Hydrochloride clinical benefit, and given the rare case in which generic sponsors are

willing to make "a significant time commitment and an investment of some magnitude" to conduct the clinical studies to ensure continued patient access to this important therapy, FDA should consider the financial contribution of Apotex, one of the holder of an ANDA Midodrine Hydrochloride as evidence that the study was "conducted or sponsored by the applicant." Without such an assurance, generic Midodrine Hydrochloride sponsors might not be willing to invest in the Phase 4 studies FDA required the NDA holder to conduct, and "patients then lose access to the drug, and may suffer serious consequences." H.R. Rep. 105-43 (errata), Prescription Drug User Fee Reauthorization and Drug Regulatory Modernization Act of 1997 4 (1997) (statement of Sen. Paul Wellstone (D-MN) made during consideration of the withdrawal of approval procedures in legislation that was eventually enacted as FDC Act § 506 – Fast Track Products).

6. **If studies are completed and certain holders of approved ANDAs or the NDA holder does not collaborate, does FDA have authority under section 505(e) of the [FDC Act] to withdraw approval of those applications? Does FDA have such authority under any other statutory or regulatory provision? Would notice and opportunity for hearing be required before withdrawal?**

The ANDA holders who collaborate would need to be given incentive for their efforts. The FDA should withdraw the approval for the companies that do not intend to participate/sponsor the Phase IV clinical studies. There is legal authority for FDA to grant a period of 3-year exclusivity to an ANDA sponsor that is part of a collaborative effort to conduct the requisite Phase 4 Midodrine Hydrochloride studies, and that submits a 505(b) supplement. Such sponsor may then selectively waive that exclusivity in favor of other ANDA sponsors who participated in the collaborative effort. The FDA at its discretion can decide upon on the notice and opportunity for hearing before withdrawal.

Please direct any communications regarding this application to Kiran Krishnan, Manager of Regulatory Affairs US at Apotex Inc at telephone 954-384-3986 or by fax at 954-349-4233. Alternatively please do not hesitate to contact me by telephone at (416) 749-9300 ext 7889 or by fax (416) 401-3809 or by email, btao@apotex.com.


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